Symptom dimensions in individuals at Ultra High Risk for psychosis neurobiological and clinical correlates

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Symptom Dimensions in Individuals at Ultra-High Risk for Psychosis: Neurobiological and Clinical Correlates

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Abstract

The Ultra High Risk (UHR) state is a clinical syndrome that is associated with a high risk for imminent psychotic disorder. Examination of the symptoms in the UHR population using a dimensional approach could improve our understanding of the clinical and neurobiological heterogeneity within UHR samples, as it has done in schizophrenia.

Two previous studies in UHR subjects have found that the symptoms measured by the CAARMS cluster on to underlying psychopathological dimensions. Moreover, both found a link between severity of scores on negative and disorganised factors and the risk of later transition to psychosis. However, one study described five symptom dimensions whereas the other described a three dimensional model, and neither structure has been independently replicated.

In the present study, CAARMS data from a total of 461 UHR subjects were used to perform principle axis factoring (PAF) and confirmatory factor analysis (CFA). Scores for each factor of the structure found to best fit the data were then correlated with resting regional cerebral blood flow (rCBF) at presentation and with clinical outcomes after two years of follow up.

PAF revealed a five factor structure, which was confirmed using CFA. In the subsample of subjects who were studied with neuroimaging, scores on the disorganisation factor were associated with reduced rCBF in the thalamus, scores on the anxiety factor were associated with reduced rCBF in the insula, and Total

CAARMS scores were associated with reduced rCBF in the left hippocampus. Higher scores on the anxiety factor and a higher total CAARMS score were associated with an increased risk of later transition to psychosis, while higher scores on the disorganisation factor was associated with worse functional outcome. These findings suggest that symptom dimensions in the UHR state have distinct neural substrates and clinical correlates. Variation in these dimensions may contribute to the marked heterogeneity of clinical presentations and outcomes within samples of UHR subjects.

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Statement of Work

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I was responsible for the recruitment of participants and data collection and data entry for the Wellcome Study. Data from the MRC study was provided by Paul Allen, and data from the EU study was provided by the EUGEI publication committee, Philip McGuire, Lucia Valmaggia, Matthew Kempton and Mark Van der Gaag.

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1 Introduction

1.1 Ultra High Risk for Psychosis

1.1.1 Early Intervention in Psychiatry

Over the last several decades there has been an increased focus on early intervention in psychiatry (Birchwood et al., 1998; Edwards & McGorry, 2002; Falloon, 1992); alongside prevention and health promotion, early intervention has been found to be an effective and efficient response to mental health needs (Falloon, 1992; Herrman, 2014; McGorry et al., 2008). In the field of psychotic disorders, symptoms preceding the onset of a psychotic episode have long been recognised (Beiser, 1993; Sullivan, 1927) and due to the strong correlation between duration of the illness and poor prognosis or outcome (Harrigan et al., 2003; Marshall et al., 2005; Perkins et al., 2005), focus has been directed towards identifying and treating this potentially prodromal stage, in order that a patient's presenting mental state might be prevented from deteriorating and the possible onset of psychosis might be delayed, lessened in severity or even prevented (H. J. Jackson & McGorry, 2009; McGorry et al., 2001; Yung et al., 1998).

McGlashan (1988) noted that the progression of symptoms in psychosis was not linear and appeared to plateau after an initial period of deterioration – the plateau effect. This idea was developed further by Birchwood et al. (1998), who described the period preceding the plateau as the "critical period": a period of rapid symptomatic, functional and psychological decline, and the period in which

intervention may offer “major opportunities for secondary prevention of the impairments and disabilities that accompany psychosis”.

More recently, Raballo and Larøi (2009) further examined the critical period, breaking it down in to a four stage clinical model, on a continuum of increasing risk, gradually progressing towards a diagnostic classification of first episode of psychosis. Moreover, increased duration of untreated psychosis has been shown by Crumlish et al. (2009) to be associated with lower odds of remission, severity of positive psychotic symptoms, worse social functioning, and poor psychosocial outcome. These factors clearly highlight the importance of intervention as close to onset as possible.

Early studies examining the effectiveness of identification and intervention at this stage (Addington et al., 2007) have found improved outcome, and reduction of risk of relapse and rehospitalisation (Linszen et al., 1998; McGlashan, 1998; McGlashan & Johannessen, 1996) prompting further investigation as to best use of resources, as well as clarification of the clinical characteristics, presentation and prognosis of the prodrome

1.1.2 Ultra High Risk for Psychosis

Yung and McGorry (1996a) examined the potentially prodromal period of disturbance preceding a first psychotic episode, primarily characterised by the emergence of clinical symptoms and altered functioning, and its potential importance for early intervention.

They noted that the symptoms present in the prodromal period are not specific to psychosis, and include symptoms of depression, anxiety, and social withdrawal (Yung & McGorry, 1996b); whilst psychotic-like experiences also occur in the general population and are not in themselves indicative of imminent psychosis (Yung et al., 2006). This means that more stringent criteria are needed to correctly identify those at risk and lower the chances of being deemed at risk unnecessarily.

They used a "close-in strategy" to identify a combination of genetic and clinical risk factors that pose an imminent high risk for psychotic disorder (Yung & McGorry, 1996a). Through a combination of interviews with first episode patients in recovery after a first acute episode of psychosis and exploration of literature of past and current conceptualisations, they investigated the period leading up to psychosis. This highlighted confusion as to the nature of prodromal features and concerns regarding the reliability of their measurement, and thus they advised for the development of a methodology for systematic evaluation and measurement of a psychotic prodrome.

Yung and McGorry described the descriptive and qualitative aspects of this putative prodromal phase, associated with a wide range of symptoms: as well as 'attenuated' (i.e. less severe) forms of psychotic symptoms that are evident in psychotic disorders, there may also be symptoms that are associated with non-psychotic conditions, such as depressive and anxiety symptoms, and personality disorders.

Raballo and Larøi (2009) argue that where the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association, 2000) and

The ICD-10 classification of mental and behavioural disorders (ICD-10) (World Health Organisation, 1992) do not describe a clear diagnostic framework for subthreshold symptomatology characteristic of the early phases of psychosis, the clinical staging model, incorporating the UHR state will give a clearer picture of the progression towards psychosis. Through the study of the UHR state and presenting symptomatology, the work presented in this thesis aims to contribute to the predictive model and identification of clinical vulnerability for psychosis.

There are two semi structured interviews used to measure symptoms and determine UHR status: the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005), developed in the Personal Assessment and Crisis Evaluation (PACE) clinic in Melbourn, used in Australia, Europe and Asia; and the Structured Interview for Prodromal Syndromes (SIPS) and Scale of Prodromal Symptoms (SOPS). The SIPS and SOPS were developed by the Prevention through Risk Identification, Management, and Education (PRIME) prodromal research team at Yale University and are used in North American Studies (Miller et al., 1999).

The CAARMS and the SIPS address the same construct and use similar criteria, however they differ on: psychopathological definitions of the Attenuated Psychotic Symptoms (APS), time and frequency criteria, functional decline criteria, Breif Limited Intermittent Psychosis (BLIPS) criteria, and assessment of comorbidities and substance misuse. Despite this, they have been shown by Fusar-Poli et al., (2016) to have very high diagnostic comparability and substantial agreement in the identification of UHR subjects. For this study, subjects were assessed using the CAARMS.

1.1.3 Comprehensive Assessment of At-Risk Mental States

The CAARMS (Yung et al., 2005), was designed to incorporate reliable methodology to clearly differentiate categorical criteria for identification and intervention in the psychosis prodrome (shown in full in Appendix 1). It examines clinical psychopathology thought to be continuous with psychosis, both positive symptoms, on which UHR status is determined, as well as affective symptoms and psychopathological domains such as: cognitive changes, emotional disturbances, negative symptoms, behavioural changes, motor and physical changes, and general psychopathology. According to Yung et al. (2005), it has two aims:

(i) To assess psychopathology thought to indicate imminent development of a first-episode psychotic disorder;

(ii) To determine if an individual meets criteria for being at UHR for onset of first psychotic disorder.

The CAARMS assesses clinical features using specialised semi-structured interviews, and to meet UHR criteria, at least one of the following conditions must be met:

(i) Group 1: Attenuated Psychotic Symptoms (APS) sub-threshold in frequency or intensity

(ii) Group 2: Brief Limited Intermittent Psychotic Symptoms (BLIPS) that resolved within a week without use of anti-psychotic medication

(iii) Group 3: Genetic risk combined with a significant recent decline in functioning.

By identifying the UHR state thorough CAARMS criteria, it may be possible to find a clinically useful and predictive model of the development of psychotic disorders. Although not all patients who meet UHR criteria go on to develop a psychotic disorder, many studies have found a significantly increased risk of developing a psychotic disorder compared to the general population (Ruhrmann et al., 2003; Yung et al., 2003) with the rate of transition to psychosis has been found to vary from 13% (Miller et al., 2003) to 50% (Haroun et al., 2006) in the first 12 months.

1.1.4 Transition to Psychosis

A meta-analysis by Fusar-Poli et al. (2012) established a transition rate of 22% over the first 12 months and up to 29% after two-years. A meta-analysis of the incidence in the general population published the same year, estimated the occurrence of psychosis in 31.7 per 100,000 people per year (95%CI: 24.6–40.9) (Kirkbride et al., 2012); thus, this represents over 700 fold increase compared to the general population making the UHR an extremely powerful and interesting research paradigm for understanding the early stages of psychosis.

However due to the high false positive rate, it is necessary to differentiate the heterogeneous sample in order to focus intervention where needed and make research in this area valuable. Several studies have looked at the effectiveness of intervention in the UHR population (McGorry et al., 2009; Morrison et al., 2004; Ruhrmann et al., 2010a), however this raises ethical and resource issues such as over use of antipsychotic treatment and the stigma of mental health diagnoses, leading to questions of whether intervention at this level is warranted (De Koning et al., 2009) given that the majority of cases will not develop a psychotic disorder.

Thus further distinction is needed in order to distinguish those who truly are experiencing the prodrome of a psychotic episode.

A categorical approach aims to differentiate the UHR sample on the basis of UHR criteria subgroups, such as the seven subgroups into which the CAARMS is split (positive, cognitive, emotional, negative, behavioural, motor/physical and general), or individual symptoms. Several studies have found positive symptoms such as unusual thought content and perceptual abnormalities are associated with later transition (Haroun et al., 2006; Ruhrmann et al., 2010b), whilst others have found that negative symptoms such as depression have a stronger link to transition (Lencz et al., 2004; Yung et al., 2003). This implies that, as suggested by Liddle (1987) and Peralta et al. (1992) the positive-negative dichotomy may not be sufficient to explain the variance of symptoms and that there may be clusters of symptoms that are phenomenologically and clinically different, with different trajectories and risk of transition.

1.2 Symptom Dimensions

1.2.1 A Dimensional Approach

The categorical approach to psychiatric disorders originated from Kraepelin's concept of "natural disease units" (natürliche Krankheitseinheiten) (Berrios & Porter, 1995) and proposes that mental disorders can be defined as distinct phenomena, and studied and treated as such. It has remained the foundation for

diagnosis and psychiatric research, and categorical diagnoses are used to study the genetics, neural basis, and treatment of psychiatric disorders (Heckers, 2011).

A dimensional approach argues that a Kraepelinian categorical approach such as that used in the DSM-IV and ICD-10, where diagnosis is determined on the basis of symptoms and characteristics typical of a disorder into discrete and distinct disorders, does not accurately represent clinical presentation. Such a categorical approach does not take into account that significant overlap may exist between different diagnostic categories, while imposing categories on dimensional phenomena may lead to a simplistic picture, missing valuable clinical information, due to the need to achieve diagnostic reliability (Brown & Barlow, 2009).

Proponents of a dimensional approach do not argue that the categorical approach is invalid, rather that it can be complemented by a dimensional approach. In particular, that examination of psychopathological syndromes or dimensions not categorically defined may give a more representative picture of symptomatology, which in turn may be of better use to determine course and outcome.

This has been found in psychosis in studies such as (van Os et al., 1996) who noted that a dimensional representation of symptoms was of better prognostic use in a cohort of cross diagnosis patients admitted with functional psychosis, accounting for associations with outcome independent of diagnosis. This association of symptom dimensions and course, outcome and treatment response, irrespective of diagnosis has since then been confirmed in many other studies (Marengo et al., 2000; Peralta et al., 2002; Rosenman et al., 2003; Sato et al., 2004)

The recent fifth edition of DSM - DSM-5 introduces an integration of a dimensional approach to diagnosis and classification with the categorical approach. Previous editions of DSM used a strictly categorical model requiring a clinician to determine that a disorder was present or absent. The dimensional approach, which allows a clinician to assess the severity of a condition and does not imply a concrete threshold between "normality" and a disorder, is now incorporated via select diagnoses.

The dimensional approach may therefore offer a better understanding of presenting symptoms and characteristics of illness, and may be useful in examination of the symptomatology of psychosis to give a clearer picture of the phenomenology and progression.

1.2.2 Symptom Dimensions in Psychosis

Underlying clusters or symptom dimensions have long been established in psychosis. In 1987, Liddle suggested that the psychopathology of psychosis may be best represented by three underlying symptom dimensions - positive (reality distortion, delusions and hallucinations), negative (poverty of speech, flatness of affect and decreased spontaneous movement) and disorganised (disorders of the form of thought and inappropriate affect). Liddle argued that these three dimensions represent three distinguishable, but related neuropathological processes in schizophrenia. This three factor model has been confirmed in subsequent studies (Andreasen et al., 1995; Liddle et al., 1992; Mortimer et al., 1990; Peralta et al., 1992), and the associations with clinical presentation, neurobiology and outcome have been investigated showing distinct

neuropsychological correlates (O'Leary et al., 2000), patterns of cerebral blood perfusion (P. F. Liddle et al., 1992) and varying course and outcome (Arndt et al., 1995).

However, more recently, several studies have found alternative models of four (McIntosh et al., 2001), five (Dikeos et al., 2006; Lindenmayer et al., 1995a; McGorry et al., 1998) and seven factor models (van Os et al., 1996), creating an inconsistent picture and Peralta and Cuesta (1999) suggest that the structure of psychotic symptoms is more complex than was previously acknowledged.

1.2.3 Symptom Dimensions in UHR

As has been found in psychosis (Liddle, 1987; Peralta & Cuesta, 1999; Van Os et al., 2009) presentation of an inconsistent picture of both three and five factor models has been found in the UHR population. Four studies have examined symptom dimensions in this population: two using SOPS, two using CAARMS.

Hawkins et al. (2004) performed a factor analysis on the Scale of Prodromal Syndromes (SOPS) finding an underlying 3 factor model, grouping roughly in to negative, disorganised and general factors. This was replicated by Fernández et al. (2006) who found a similar three factor structure in SOPS.

There have been two studies that have looked at the symptom dimension in UHR using the CAARMS. Demjaha et al. (2010) used principle axis factor analysis and found a five factor underlying structure, accounting for 37% of the total variance (sample size = 122). The five factors were Disorganised, Negative, Anxiety, Self-

Harm and Affective Instability. Disorganised and Negative factors were found to be predictors of transition to psychosis.

Raballo et al. (2011) used principal component analysis and found a three factor underlying structure accounting for 39% of the total variance (sample size = 223). The three factors were: negative/interpersonal, communication/cognitive/behavioural disorganisation, and perceptual/affective instability. The disorganised factor was the strongest predictor of transition to psychosis.

Using factor analyses, Demjaha et al. and Raballo et al. both report symptom dimensions that may be useful for predicting transition to psychosis, however, despite using similar recruitment pathways through clinical services in community based catchment areas these studies report conflicting three and five factor structures based on different samples in different geographical locations.

Despite inconsistent findings for the number of included factors, the underlying factor structure of baseline presenting symptoms seems to be a consistent feature of both psychosis and UHR states and has been shown to have an association with longitudinal outcome in UHR. However, as yet, neither of the underlying three or five factor structures described above have been replicated in an independent UHR sample and the disagreement between factor structures outlined above shows that further investigation is needed to establish if these factors are generalizable across samples and have temporal stability across time points.

This project will explore whether the five factor structure found by Demjaha et al. (2010), the three factor structure found by Raballo et al. (2011) or a different structure all together fits CAARMS symptom data from a new, independent cohort of 512 UHR subjects recruited from clinical centres in the UK, Netherlands, Austria, Switzerland, France, Spain, Turkey, Australia, Belgium, Germany and Brazil. This will be done using Confirmatory Factor Analysis (CFA) and Exploratory Factor Analysis (EFA).

1.3 Neurobiology of Symptom Dimensions

1.3.1 Neurobiology of Symptoms Dimensions in Psychosis

The heterogeneity in symptom presentation and wide range of courses and outcomes in schizophrenia complicates the search for neurobiological substrates of the disorder. It may therefore be more beneficial to examine neural correlates using a dimensional approach – refining analyses to look at groups of presenting symptoms, rather than a categorical approach, combining all symptoms under the diagnostic category of schizophrenia. Division of a sample by phenotypic variation can be used to form subgroups, which are more homogeneous and therefore may enable a more simple and accurate investigation of neural pathology.

Liddle et al. (1992) argued that the clinical heterogeneity of schizophrenia must reflect the heterogeneity in underlying neuropathology. After having established and replicated the three distinct syndromes (Liddle, 1987; Liddle & Barnes, 1990) (positive (reality distortion, delusions and hallucinations), negative (poverty of

speech, flatness of affect and decreased spontaneous movement) and disorganised (disorders of the form of thought and inappropriate affect)), Liddle and colleagues went on to examine their neurobiological correlates. Using Positron Emission Tomography (PET), they examined regional brain activity through measuring Cerebral Blood Flow (CBF), and found that the three distinct syndromes described above, were each associated with different patterns of CBF. More notably, the neuronal dysfunction fit with the specific predictions based on the clinical and neuropsychological characteristics of each syndrome (P. F. Liddle et al., 1992).

The distinct neuroanatomical alterations associated with the established three syndromes in schizophrenia have been subsequently replicated in many studies. Nenadic et al. (2010) found distinct grey matter abnormalities associated with positive, negative and disorganised symptoms, and further established that the pattern of regionally distributed alterations in brain structure would provide sufficiently accurate classification (95.8%) of a given scan to be assigned to the schizophrenia subgroup as determined by psychopathology. While Goghari et al. (2010) reviewed 25 task based fMRI studies examining the relationship between symptom dimensions and regional brain activity and found distinct patterns of neural function according to positive, negative and disorganised symptoms, providing consistent links between the manifest symptoms of schizophrenia and brain dysfunction.

More recently, Cerebral Blood Flow (CBF) has been examined using arterial spin labelling (ASL) perfusion MRI - a technique that allows for quantitative measurement of CBF by using magnetically labelled arterial blood water as an

endogenous tracer. Pinkham et al. (2011) used this technique to distinguish differences in CBF associated with positive and negative symptoms. Severity of negative symptoms was associated with reduced CBF in bilateral superior temporal gyrus, cingulate gyrus, and left middle frontal gyrus, while severity of positive symptoms was related to both higher CBF in cingulate gyrus and superior frontal gyrus and decreased CBF in precentral gyrus/middle frontal gyrus.

1.3.2 Resting Cerebral Blood Flow in Ultra High Risk

Recently animal models have been used to help understand the neurobiological mechanisms underlying the development of psychosis. Preclinical models such as the methylazoxymethanol acetate (MAM) Model, posit a key role for the hippocampal-midbrain-striatal circuit in the development of psychosis, and suggest that prior to onset of psychosis in humans, resting hippocampal activity may be elevated (Lodge & Grace, 2011). In keeping with this, several studies have shown reduced hippocampal volume and increased hippocampal perfusion in subjects meeting UHR criteria (Mechelli et al., 2011; Pantelis et al., 2003; Schobel et al., 2009).

Resting hippocampal activity can be assessed by measuring resting cerebral blood flow (rCBF), which allows for an indirect gauge of neural function (Hirano et al., 2011). This can be measured using pseudo-Continuous Arterial Spin Labelling (p-CASL), and allows for the mechanism proposed in the MAM model to be directly investigated in subjects at high risk for psychosis. Recent studies such as Allen et al. (2016) have shown in a longitudinal study of UHR subjects, that as well as resting state hyperperfusion evident in the hippocampus, midbrain, and basal ganglia of

UHR subjects at onset of symptoms, this perfusion reduces in line with subsequent symptomatic improvement. Reduced rCBF in the hippocampus and ventral striatum were observed at follow-up for those showing symptomatic improvement and subjects whose symptoms had resolved and no longer met ultra-high-risk criteria showed a reduction in left hippocampal rCBF not present in subjects who transitioned to psychosis, or who still met Ultra High Risk criteria.

These findings confirmed the findings of a previous study, measuring rCBF using a steady-state gadolinium-enhanced fMRI technique rather than ASL by Schobel et al. (2009), and provide evidence that increased resting hippocampal activity described in preclinical models can be applied to the psychopathology of psychosis.

1.3.3 Neurobiology of Symptom Dimensions in Ultra High Risk

As described above, perfusion alterations are a consistent finding in UHR studies, in keeping with the developmental mechanisms described using the MAM model. Additionally, although early evidence in schizophrenia using PET (P. F. Liddle et al., 1992) and more recent examination using MRI (Pinkham et al., 2011) has shown that different patterns and regions of perfusion can be distinguished according to symptomatic presentation, this has not yet been investigated in the UHR population.

After having used factor analysis to establish if a dimensional representation of symptoms is applicable in the UHR population, this study will go on to investigate the neurobiological correlates of these dimensions through measuring resting Cerebral Blood Flow, using MRI to give a picture of neural rCBF (perfusion) associated with different types of symptoms. This may be able to give a biological

validation to statistically determined dimensions, and contribute to the understanding of the distinct cause, course and outcome associated with each of them.

1.4 Clinical Application of Symptom Dimensions

1.4.1 Symptom Dimension and Clinical Presentation/Outcome

In order to clarify the degree to which psychotic symptoms are predictive of course and outcome of illness, it is necessary to relate dimensions longitudinally to clinical and functional follow-up data. Association of dimensions with various illness characteristics regarding onset, course and impairment has been reported in a number of studies in both psychosis (Owens et al., 2010; van Os et al., 1996; Wickham et al., 2001) and UHR (Demjaha et al., 2010; Johnstone et al., 2005; Raballo, 2011; Ziermans et al., 2014).

The relationship between symptom dimensions and outcome has been examined in psychosis extensively, with many studies concluding that symptom dimensions prove to be a more powerful tool in explaining variance of outcome than categorical sub-diagnoses (Salokangas, 2003).

Negative symptoms have been consistently linked with poor outcome in psychosis. In studies which examined the correlation between psychopathological dimensions and clinical characteristics, the negative factor was found to be associated with poor premorbid functioning (Wickham et al., 2001) earlier or insidious onset (Sato et al., 2004; van Os et al., 1996) or deteriorating/chronic course of illness (Levine &

Leucht, 2013; Sánchez-Torres et al., 2017). Disorganised symptoms have similarly been linked to poor functional outcome (Ortiz et al., 2015) and risk of remission (Owens et al., 2010).

In order to examine the relationship between dimensions and outcome in the UHR population, we must ascertain definitive outcome measures, as this group does not have a categorically defined diagnosis or course of illness.

Traditionally the outcome measure in UHR has been risk of transition to psychosis, as this is the predominant aim in defining the UHR criteria, with an average transition rate of around 29% in the following 2 years (Fusar-Poli et al., 2012). However, meeting UHR criteria, although indicative of a significant increase in risk for developing psychosis compared to the general population (Kirkbride et al., 2006), is not indicative of a psychosis prodrome in the majority of subjects, and it is therefore important to determine outcome not only according to transition.

There has been recent support for the increasing emphasis on functional decline as a critically important outcome to be considered alongside the rate of transition to psychosis (Cornblatt et al., 2012; Schlosser et al., 2012). The identification of factors that reliably differentiate UHR subjects that are at high risk for long term functional impairments from those who are not may provide a framework to understand the disability associated with both those who transition and those who do not.

The link between severity of negative symptoms and poor outcome in psychosis has been confirmed in UHR by three studies examining symptom dimensions and outcome in UHR (Demjaha et al., 2010; Hawkins et al., 2004; Raballo et al., 2011),

all finding negative symptoms linked to increased risk of transition to psychosis. Demjaha et al. (2010) and Hawkins et al. (2004) also found a link between severity of disorganised symptoms and subsequent transition to psychosis. However, to date, no studies have examined the relationship between symptoms in UHR and functional outcome.

1.5 Aims and Objectives of this Study

This study will examine three main objectives in three distinct empirical chapters.

Chapter 2 will present the current literature and theoretical framework behind symptom dimensions in psychosis and its application in UHR. It will then go on to examine the symptom dimensions present in a large multi-site sample of UHR subjects recruited from 13 centres in Europe, South America and Australia between 2010 and 2016, in two factor analyses: an exploratory factor analysis to determine the structure present in this sample and a confirmatory factor analysis to compare the model fit of the structure found and the two structures previously found in the literature. The total sample comprises data from a wide range of clinical centres and as such may provide a sample that is more representative of the UHR subjects who present to such services rather than a sample derived from a single centre.

Chapter 3 will present the neurobiological findings in psychosis and UHR with a specific focus on the neural correlates of symptoms and symptom dimensions. Resting cerebral blood flow will then be examined using MRI data in a subset of the

sample from London to determine the relationship between symptom dimensions and cerebral resting perfusion in UHR subjects.

Finally, chapter 4 will present the current findings relating to presenting symptomatology, other clinical variables and longitudinal outcome data. The possible definitions of outcome in the UHR population will be considered, and how these are of clinical and research use. Regression analyses will be conducted in order to determine the relationship between the severity of scores on each symptom dimension and clinical outcome.

Specific hypotheses will be outlined in their respective chapters.

2 Symptom Dimensions in individuals at Ultra High Risk for Psychosis

2.1 Introduction

2.1.1 Heterogeneity in Ultra High Risk for Psychosis

An individual can meet the CAARMS criteria for the UHR state if their clinical features satisfy the inclusion criteria for one of three distinct (but not mutually exclusive) domains: Attenuated Psychotic Symptoms (APS), Brief Limited Intermittent Psychosis (BLIP), and Genetic Risk combined with a recent functional decline. Despite the majority of UHR meeting criteria for APS, the symptomatology in UHR subjects varies between individuals, and between samples, depending on which of the different types of inclusion criteria are met. The UHR state is also associated with a high prevalence of non-psychotic symptoms, with up to 70% of subjects meeting criteria for another comorbid psychiatric diagnosis (particularly depression and anxiety) in addition to the UHR state (Fusar-Poli et al., 2012). Again, the presence of comorbid diagnoses varies between UHR subjects, and between UHR samples.

Variation in the presenting symptomatology between centres may contribute to the differences in the rates of transition to psychosis reported from different sites, with some describing rates as high as 40-50% (Miller et al., 2002; Yung et al., 2003) but others rates as low as 10% (Demjaha et al., 2010; Haroun et al., 2006). This variability also applies to clinical outcomes among the UHR subjects who do not go on to develop psychosis, with between-site differences in the proportions of subjects who no longer meet criteria for the UHR state at follow up ranging from

15% (Miller et al., 2002) to 54% (Velthorst et al., 2011). A key factor underlying these differences is that the way UHR subjects are ascertained varies substantially between sites: some centres provide a full clinical service for UHR subjects, but others only recruit subjects to take part in research projects, and do not offer clinical care. There are also wide variations in the clinical presentation and intake group (Attenuate Psychotic Symptoms/Brief Limited Intermittent Psychosis/Genetic Risk and Functional Decline) of the individuals enrolled at different centres, as shown by Fusar-Poli et al. (2016), who found significant differences between studies in a meta-analysis of longitudinal UHR studies and significant differences in transition rate according to intake group, although the predominant intake groups was consistently APS.

2.1.2 Comprehensive Assessment of At Risk Mental State (CAARMS)

The CAARMS consists of 27 items that are designed to assess the psychopathology associated with the UHR state. However these items do not correspond to 27 independent symptoms: many of them are highly inter-correlated. Examining symptom dimensions, as opposed to individual symptoms, provides a way of assessing how individual symptoms cluster together on common dimensions. It is possible that symptom dimensions are more closely related to etiological and pathophysiological risk factors for the UHR state than individual symptoms (Liddle, 1987; P. F. Liddle et al., 1992). Similarly, variation in symptom dimensions may be more closely linked to variation in clinical outcomes in UHR subjects than differences in individual symptoms (Van Os et al., 2009).

The CAARMS is divided in to 7 subgroups of symptoms. Although these correspond to different kinds of symptoms (Positive, Cognitive, Emotional, Negative, Behavioural, Motor/Physical, and General), the basis of the subdivision is theoretical rather than empirical. In contrast, symptom dimensions reflect the statistical probability that subsets of different symptoms cluster together. By identifying such dimensions, factor analysis can reduce the number of observed variables (in this case symptoms) into a smaller number of latent variables (in this case symptom dimensions) by examining the covariation among the observed variables. This reveals a structure that reflects the underlying data, as opposed to a theoretical construct.

2.1.3 Examination of Symptoms in UHR

Factor analyses of symptoms in patients with psychosis initially produced a three factor model, consisting of positive, negative and disorganised factors (Liddle, 1987) which was widely replicated (Andreasen et al., 1995; Mortimer et al., 1990; Peralta et al., 1992). However, more recent analyses suggest that the structure of psychotic symptoms is more complex than was previously acknowledged (Peralta & Cuesta, 1999; Van Os et al., 2009).

In UHR data, Hawkins et al. (2004) performed a factor analysis in 94 subjects assessed using the Scale of Prodromal Syndromes (SOPS) and found a 3 factor model, comprising negative, disorganised and general factors. The three factors found in UHR models are similar to the model found in psychosis; however they lack the distinct positive factor, and instead had a general factor.Fernández et al. (2006) also found a similar three factor structure based on use of the SOPS in 30

UHR subjects. A three factor model was also found by Comparelli et al. (2011) in the Italian version of SOPS , however this differed from the previous two three factor structures and a study published in the same year found a contrasting four factor structure (Klaassen et al., 2011). The sample size used in the Comparelli et al. (2011) study was the largest sample (n = 128), and although the minimum sample size, or the minimum ratio of sample size to the number of variables, is variant across studies (MacCallum et al., 1999), this does not meet the rules of thumb for the minimum sample size necessary to obtain factor solutions that are adequately stable and that correspond closely to population factors. These small sample sizes may contribute to the variation in structures found.

Two studies have looked at the symptom dimension in UHR state using the CAARMS. The CAARMS differs from the SOPS in some of the operational criteria such as time and frequency criteria, functional decline criteria and most notably in BLIPS criteria, where the SIPS considers “seriously disorganizing or dangerous” features as fully psychotic, whereas under CAARMS criteria, these are deemed UHR. Despite this, they have been shown by Fusar-Poli et al. (2016) to have very high diagnostic comparability and substantial agreement in the identification of UHR subjects. The two CAARMS models are described below.

2.1.4 A Five Factor Model

Demjaha et al. (2010) used principle axis factor analysis of CAARMS data and found a five factor underlying structure, accounting for 37% of the total variance (sample size = 122). The five factors were Disorganised, Negative, Anxiety, Self-Harm and Affective Instability. Nineteen of the Twenty-seven CAARMS items were included,

the five factors and the items that load on them, are shown in figure 1 below. One item (Observed Changes in Motor Functioning) was excluded as it was present in less than 10% of the sample, and seven items (OCD Symptoms, Impaired Bodily Sensation, Aggression/Dangerous Behaviour, Unusual Thought Content, Perceptual Abnormalities, Dissociative Symptoms, Observed Inappropriate Affect and Changes in Motor Functioning) were excluded because they did not have a robust loading of over 0.4 on any factor. The Disorganised and Negative factors were found to be predictors of subsequent transition to psychosis, as determined from clinical follow up at 24 months.

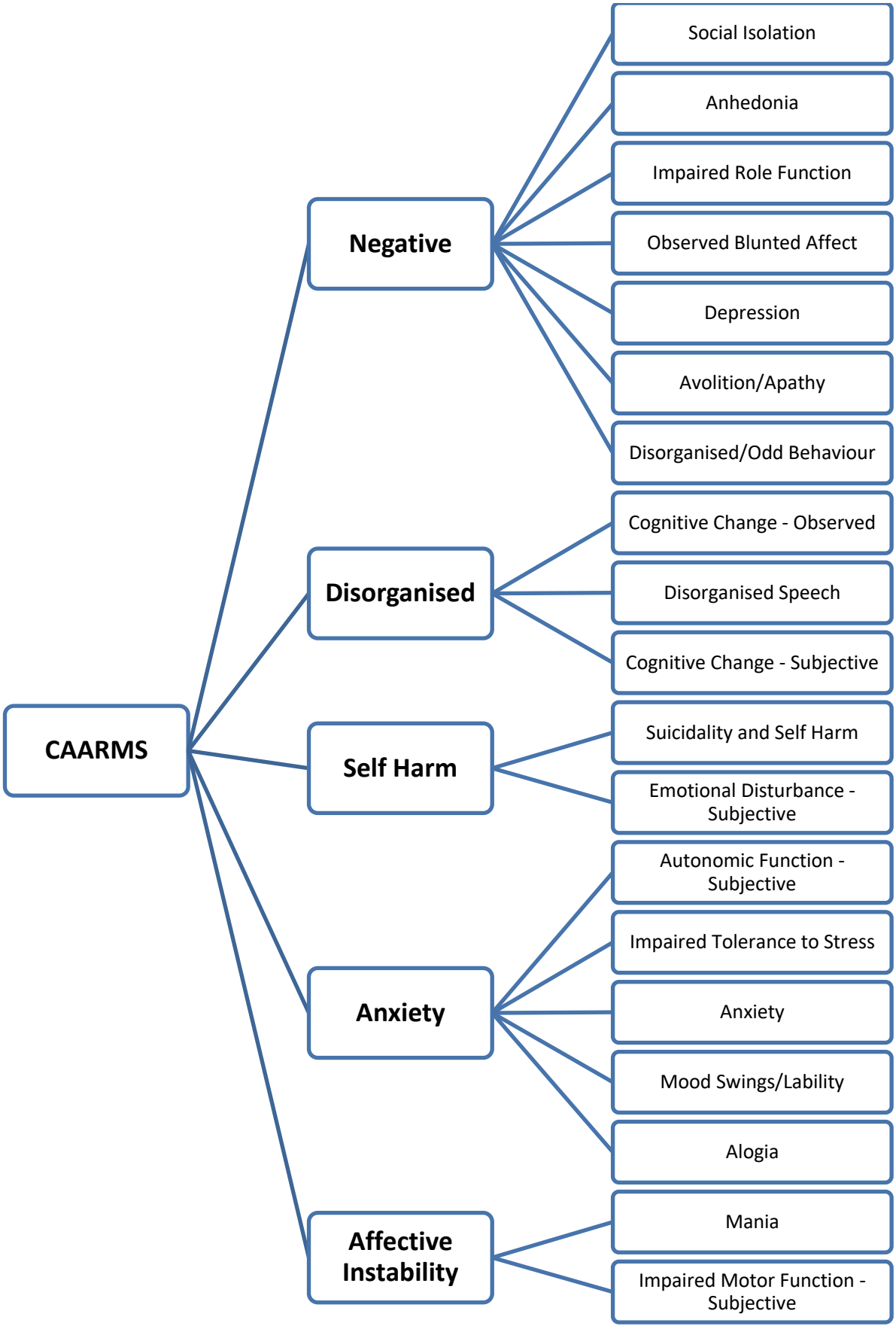

Figure 1: Five Factor Model of 19 CAARMS symptoms found by Demjaha et al. (2010)

2.1.5 A Three Factor Model

Raballo et al. (2011) used principal component analysis in 223 UHR subjects with symptoms assessed using the CAARMS. They described a three factor structure that accounted for 39% of the total variance in all twenty-seven items at baseline. This included items with loadings over 0.3. The 3 factors were: negative/interpersonal, communication/cognitive/behavioural disorganisation, and perceptual/affective instability, and are shown in figure 2. Clinical follow up revealed that higher scores on the disorganised factor were associated with later transition to psychosis at 12-month follow up.

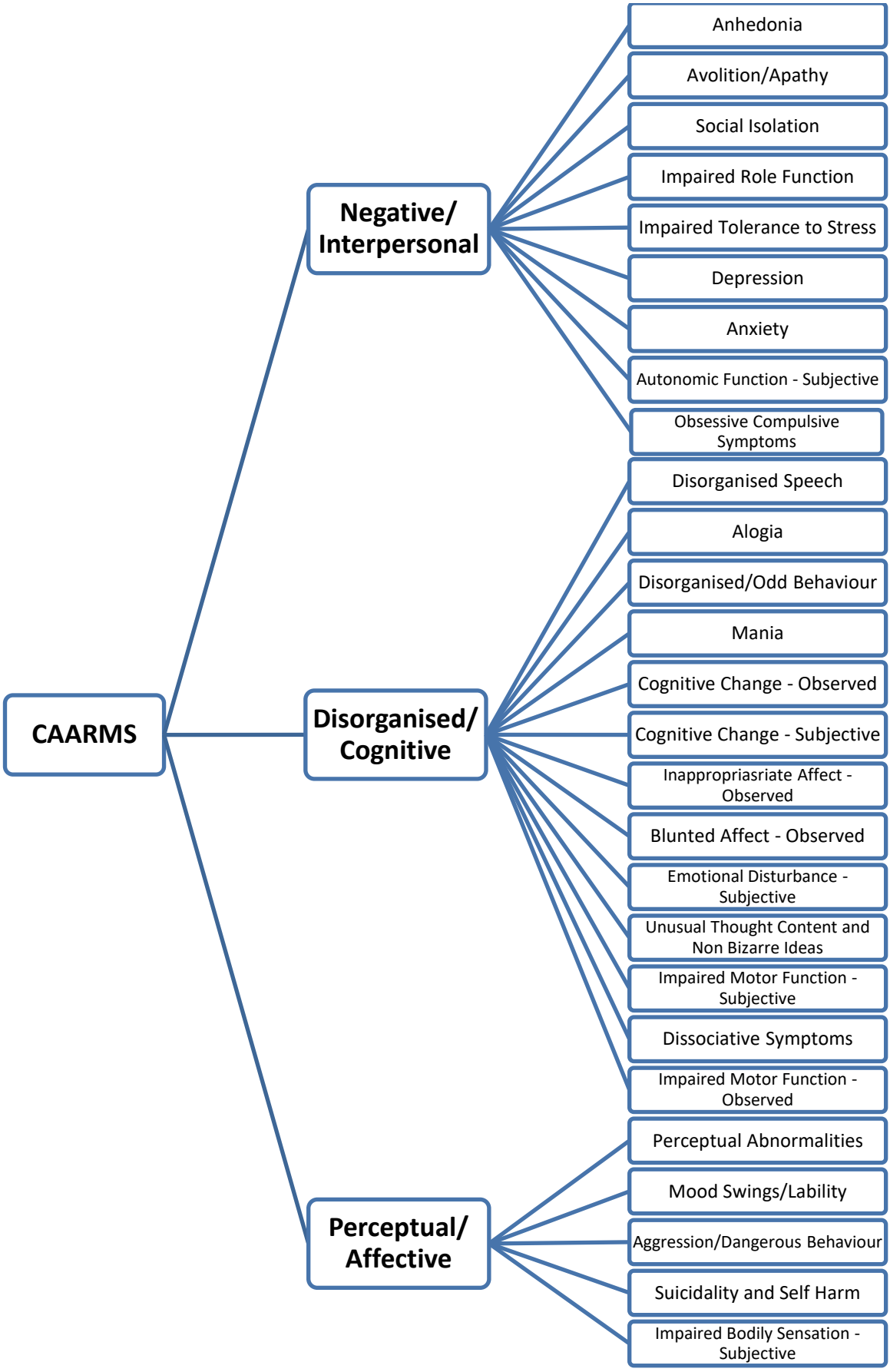

Figure 2: Three Factor Model of 27 CAARMS Symptoms found by Raballo et al. (2011)

Both Demjaha et al. and Raballo et al. reported that scores on particular symptom dimensions may be associated with the risk of later transition to psychosis. However, the former identified a five-factor structure, and the latter only three. Although both studies recruited participants through catchment based clinical services, it is not clear to what extent this indicates differences in the symptomatology in the respective UHR samples from each site, reflecting the presence of different subtypes of UHR individual, which might be associated with different aetiologies, pathophysiologies and clinical outcomes. To date, neither a three or a five factor structure has been replicated or confirmed in an independent UHR sample.

This thesis aimed to address this issue by examining the factor structure of CAARMS symptom data in a cohort of 512 (over double that used in the previous studies) UHR subjects recruited from centres in the UK, Netherlands, Austria, Switzerland, France, Spain, Turkey, Australia, Belgium, Germany and Brazil, using Confirmatory Factor Analysis (CFA) and Exploratory Factor Analysis (EFA).

2.1.6 Factor Analysis

Both EFA and CFA permit investigation of the relationship between observed measures (in this case scores on the 27 items of the CAARMS questionnaire), and latent variables, factors, or underlying dimensions. A large number of observed variables can thus be reduced to a smaller set of latent variables. EFA is a data driven approach, which does not allow for the specification of any structure or relationships. Rather, it is descriptive and will indicate the structure that best fits

the data according to the correlations and covariances present. This is valuable in the earlier stages of research, before a structure has been established for an instrument. Both the Demjaha and the Raballo studies used EFA for their initial investigation of CAARMS dimensions in UHR subjects.

Whereas EFA is exploratory, CFA can be used to confirm previously established structures in new datasets, where a structure has previously been established on empirical or theoretical grounds. In the case of the present study the structures used in the CFA are the two identified in the previous UHR studies.

One disadvantage of Exploratory Factor Analysis (EFA) is that although the results show factor loadings for each item in the dataset, there are no goodness of fit indices for the resulting model making it hard to determine how well the model fits the data. However, Confirmatory Factor Analysis (CFA) allows testing of the fit of a model to any dataset. A model that has been found in one data set, but cannot be confirmed subsequently in independent data sets has limited application. Therefore the aim of the present study is to use EFA to determine a model and then use CFA in an independent dataset to compare the previously found models to determine which, if any, structure is generalizable.

The total sample comprises data from a wide range of clinical centres and as such may provide a sample that is more representative of the UHR subjects who present to such services rather than a sample derived from a single centre. The data collected from all centres will be compared to ensure statistical similarity before being pooled to create a larger sample. This approach is similar to the method used by van der Gaag et al. (2006), who used confirmatory factor analysis to test models

previously found in the literature on a large pooled dataset in which symptoms had been assessed using the Positive and Negative Syndrome Scale (PANSS). The relatively large size of the pooled sample in the present study (n=512) means that it can be split into two subsamples (UK and non-UK) to perform the exploratory and confirmatory factor analyses, respectively. This is because the two previous studies were conducted in UK (Demjaha et al., 2010) and non-UK samples (Raballo et al., 2011).

2.1.7 Aims and Objectives of this Study

This chapter will describe a factor analysis conducted on CAARMS symptom data from a total sample of 557 UHR patients recruited from clinical centres in the UK, Netherlands, Austria, Switzerland, France, Spain, Turkey, Australia, Belgium, Germany and Brazil. This will involve splitting the data in to two, with the first half of the data used to conduct an Exploratory Factor Analysis (EFA) to determine a model, and the second used to conduct a Confirmatory Factor Analysis (CFA) to compare this model with previously found models, to determine which, if any, model is most generalizable.

2.2 Method

2.2.1 Sample

The total sample is comprised of 557 individuals meeting the PACE criteria for UHR, aged 18-35 recruited through three different studies conducted between 2008 and 2017. Fifty-three participants were recruited through an MRC funded study at

King's College London that aimed to examine neurobiological differences between UHR and healthy volunteers; ninety through a Wellcome Trust funded programme at King's College London designed to ascertain which neurobiological factors best predicted transition/outcome in UHR subjects (collected by the author); and four hundred and fourteen from an FP7 project funded by the European Union, involving sites in the UK, Netherlands, Austria, Switzerland, France, Spain, Turkey, Australia, Belgium, Germany and Brazil. A breakdown of the total sample by location is shown in table 1 below. All studies had National Research Ethics Service (NRES) approval and all participants gave written informed consent to participate.

Table 1: Geographical Composition of Total Sample

Study	Location	Number
MRC study	UK - London - South London	53
Wellcome Study	UK - London - South London	63
	UK - Cambridge	19
	UK - London - West London	8
EU Study	UK - London - South London	149
	The Netherlands - Amsterdam	20
	The Netherlands - Den Haag	69
	Austria - Vienna	8
	Switzerland - Basel	25
	Germany - Cologne	16
	Australia - Melbourne	29
	Belgium - Kortenberg/Leuwen	45
	France - Paris	21
	Spain - Barcelona	23
	Brazil - Sao Paulo	9
Total		**557**

2.2.2 Eligibility Criteria

Participants were recruited from specialist early intervention services and assessed by researchers trained to administer the CAARMS. According to the PACE criteria, an individual can be classed as UHR if they meet the threshold for one or more of the following subcategories:

Group 1: Attenuated Psychotic Symptoms (APS) sub-threshold in frequency or intensity (84%)

Group 2: Brief Limited Intermittent Psychotic Symptoms (BLIPS) that resolved within a week without use of anti-psychotic medication (11%)

Group 3: Genetic risk combined with a significant recent decline in functioning (5%)

(The decline in functioning was only an inclusion criterion in the Genetic Risk group)

In the present study, inclusion required that participants:

- Met UHR criteria
- Were aged 18 - 35

The exclusion criteria were:

- Neurological or medical illness or head injury
- Presecribed antipsychotic medication for longer than 2 weeks
- IQ lower than 70
- Meeting DSM-IV criteria for drug/alcohol abuse or dependency
- Treatment with antipsychotic medication for a week or more

2.2.3 Measures

The Comprehensive Assessment of At Risk Mental State (CAARMS) is a semi-structured interview designed by (Yung et al., 2005). It aims to measure the dimensions of psychopathology needed to meet the criteria for UHR status,

including intensity, frequency, duration and distress associated with symptoms. The 27 items[1] are categorised in to 7 sections:

1. **Positive** – including unusual thought content, non-bizarre ideas, perceptual abnormalities and disorganised speech (4 items)
2. **Cognitive Change** – including subjective cognitive change and observed cognitive change (2 items)
3. **Emotional Disturbance** – including subjective emotional disturbance, observer blunted affect and observed inappropriate affect (3 items)
4. **Negative** – including alogia, avolition/apathy and anhedonia (3 items)
5. **Behavioural Change** – including social isolation, impaired role functioning and aggression/dangerous behaviour (4 items)
6. **Motor/Physical Change** – including subjective impaired motor functioning observed changes in motor functioning, subjective impaired bodily sensation and subjective impaired autonomic functioning (4 items)
7. **General Psychopathology** – including mania, depression, suicidality and self-harm, mood swings/lability, anxiety, OCD symptoms, dissociative symptoms and impaired tolerance to normal stress (7 items)

Severity and Frequency are scored on a scale of 0-6, and distress is scored as a subject reported percentage. Sub-threshold intensity Attenuated Psychotic Symptoms are classified as a severity score of 3-5 on Unusual Thought Content and

[1] A later version updated in 2006 included 28 items - item 1.1 Unusual Thought Content and Non Bizarre ideas was split in to two items 1.1 Unusual Thought Content and 1.2 Non Bizarre Ideas. A drop in functioning was also added as additional criteria for inclusion in the APS and BLIP groups.

Non Bizarre Ideas, 3-4 on Perceptual Abnormalities, and/or 4-5 on Disorganised Speech and a frequency score of 3-6 on any of the items in the Positive scale, Sub-threshold frequency Attenuated Psychotic Symptoms are classified as a frequency score of 3 and a severity score of 6 on Unusual Thought Content and Non Bizarre Ideas, 6 on Disorganised Speech, and 5-6 on Perceptual abnormalities. A severity score of 6 on Unusual Thought Content and Non Bizarre Ideas, 6 on Disorganised Speech, and 5-6 on Perceptual abnormalities, with frequency greater than 4 on any of the items in the Positive scale is classified as Psychotic (group inclusion criteria is shown at the end of the CAARMS in Appendix 1). As in previous studies (Demjaha et al., 2010; Raballo, 2011), the Severity score was used to perform the analysis.

Participants recruited through the MRC study (n=53) completed the earlier version of the CAARMS, and therefore a drop in functioning was not a requirement for meeting APS/BLIP criteria. Participants recruited in the subsequent two studies (n=504) used the 2006 CAARMS, where the drop in functioning was required.

The CAARMS was implemented by a trained researcher at each site. Inter-rater reliability was ensured via online training tools for the CAARMS incorporating inter-rater reliability standard requirement for completion of the training. Language inconsistencies for centres not conducting assessments in English was addressed through back translation.

2.2.4 Missing Data

Listwise deletion of missing data was used - cases were dropped from analysis if they had a missing value in at least one of the specified variables. This is because

Confirmatory Factor Analysis can only be applied to cases which have a complete set of data.

There were forty five subjects who were included in more than one of the studies. Of an initial sample of 557, after removal of these subjects the sample size was 512. After removal of fifty one subjects for whom there were missing data the sample size was 461. This is roughly four times the size of the Demjaha et. al. sample and twice the size of the Raballo et. al. sample (n = 122 and 223 respectively)

2.2.5 Statistical analysis

As the data came from three different studies, an initial group comparison was performed to determine whether the respective data sets were sufficiently statistically similar to be pooled. This required that they have statistically similar subjects by age and gender, and shared the same structure of CAARMS scores, which would be expected if they represented different samples of the same population.

Once grouped together, in order to perform both the Exploratory and Confirmatory factor analyses the data set was split into two subsets – Set 1 (EFA) and Set 2 (CFA). Confirmatory factor analysis can only validate a putative factor structure if it is performed on a separate data set to the one in which the original factor structure was found (through exploratory factor analysis), to avoid cross-validation.

In the present study, the data set was split into two by location: UK (n= 235) and Non-UK (n= 226). This approach was adopted because the two previously found factor structures in UHR subjects were identified with samples from clinical centres

that were in the UK (Demjaha et al., 2010) and outside the UK (Melbourne, Australia (Raballo et al., 2011)), respectively. The UK data were used for the exploratory factor analysis to determine a structure in a unified sample from one centre and the non-UK data for the confirmatory factor analysis to see if the factor structure is generalizable to a more general multi-centre sample.

Exploratory factor analysis was conducted using SPSS (version 23) using the severity scores of all 27 CAARMS items, and factors were subjected to a promax rotation to allow for correlation between factors. Only loadings greater than 0.4 were used to determine dimensions (Comrey, 1973).

Confirmatory factor analysis was conducted using AMOS (version 23) to measure the goodness-of-fit of the alternative models. The indices used to determine goodness of fit were χ^2, Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Standardised Root Mean Square Residual (SRMR) and the Root Mean Square Error of Approximation (RMSEA). χ^2 should be close to 2, where 0 is a perfect fit, CFI and TLI should be above 0.90, where 1 is a perfect fit, SRMR should be below 0.08 and the RMSEA should be below 0.06 where 0 is a perfect fit (Schreiber et al., 2006). These are the fit indices recommended by Hu and Bentler (1999) and represent different measurement properties – absolute fit (χ^2 & SRMR) relative fit (TLI) and non-centrality based indices (CFI & RMSEA).

Absolute fit indices are derived from the fit of the covariance matrices and maximum likelihood estimation of the data set, and do not use an alternative model as a base for comparison. Chi-square (χ^2) is the original fit index for structural models and the basis for other fit indices. However it has been shown to be

affected by sample size (Marsh et al., 1988), model size (Schreiber et al., 2006) and the distribution of variables (Curran et al., 1996), so although it should be reported, it is rarely non-significant and it is recommended that other absolute fit indices be reported (Hu & Bentler, 1999). The residual based fixed index (SRMR) was therefore used as well.

Relative fit indices compare a chi-square for the current model to one from a null model. The null model is a model in which all measured variables are uncorrelated - there are no latent variables. The relative fit index used in this analysis will be TLI (Tucker & Lewis, 1973) as it has been shown to be less effected by sample size (Bollen, 1990).

Non-centrality based indices are all based on an estimation of the population non-centrality parameter. Rather than testing the hypothesis that the fit is perfect, they test how bad the model fit is, and they allow confidence interval assessment as well as cut-off points used in other indices. CFI measures incremental fit, and RMSEA measures residuals bases fit, and both RMSEA and CFI have been shown to perform well with respect to model misspecification and sample size (Hu & Bentler, 1999; D. L. Jackson, 2007; Marsh et al., 1998).

The models being tested were:

1. One factor model of all CAARMS Items
2. Three factor model from Raballo (2011)
3. Five Factor Model from Demjaha et al. (2010)

4. Seven factor model of CAARMS symptom categories (the standard symptom divisions of the CAARMS)
5. Model found following EFA of the UK data from the present Study

2.3 Results

2.3.1 Test of Homogeneity

In order to combine the three data sets, Levine's test of homogeneity of variance was performed on the CAARMS scores for the three data sets. This indicated equal variances of CAARMS scores ($F = 1.59$, $p = .205$) which suggested that the data sets could be pooled. A one way Anova showed no significant differences in age and a chi square test showed no significant differences in gender between the three samples

2.3.2 Sample characteristics

The final pooled sample consisted of CAARMS scores for 461 participants. The sample was 56% male, the mean age was 22 years and 4 months, and 57% of the subjects were white, 34% black and 9% from other ethnic minorities. 84% of the sample met the inclusion criteria for Attenuated Psychotic Symptoms (APS), 11% Brief Limited Psychotic Period (BLIP) and 5% Genetic Vulnerability. Gender, age, ethnicity and CAARMS intake group breakdowns for each sample are shown in the table 2 below.

Table 2: Characteristics of Three Pooled Samples, Combined Total Sample and Sample Split for Factor Analyses

Sample Group		Wellcome Study	MRC Study	EU Study	Total Sample	SET 1 – UK	SET 2 – Non-UK
Sample Size		90	53	414	557		
Number included*		85	50	326	461	235	226
Age	Mean	22.47	22.56	22.22	22.66	22.62	21.95
	SD	3.60	4.43	4.78	4.35	4.27	4.42
Gender (male)		48 (56%)	27 (54%)	170 (52%)	245 (53%)	123 (52%)	123 (54%)
Ethnicity	White	54 (64%)	28 (56%)	211 (65%)	293 (63%)	148 (63%)	144 (64%)
	BME	31 (36%)	22 (44%)	115 (35%)	168 (36%)	90 (38%)	78 (35%)
Intake Group	APS	79 (88%)	42 (84%)	280 (86%)	400 (86%)	207 (88%)	193 (85%)
	BLIP	6 (7%)	0 (0%)	20 (6%)	30 (7%)	16 (7%)	14 (6%)
	Genetic Vulnerability	5 (5%)	8 (16%)	26 (8%)	31 (7%)	12 (5%)	19 (8%)

* After removal of duplicate participants and listwise removal of missing data

CAARMS scores recorded in the total sample ranged from 0-6 for each item, and every item was present in at least 10% of the sample. A breakdown of scores for each item is shown in the table 3 below.

Table 3: Mean, Standard Deviation and Range of All CAARMS Items

CAARMS group	Number	CAARMS Item	Minimum	Maximum	Mean	SD
1. Positive Symptoms	1.1	Unusual thought content and non-bizarre ideas	0	6	2.66	1.53
	1.2	Perceptual abnormalities	0	6	2.82	1.82
	1.3	Disorganized speech	0	6	1.58	1.47
2. Cognitive Change Attention/Concentration	2.1	Subjective cognitive change	0	6	2.24	1.26
	2.2	Observed cognitive change	0	5	0.70	1.01
3. Emotional Disturbance	3.1	Subjective emotional disturbance	0	6	1.89	1.53
	3.2	Observed blunter affect	0	6	0.88	1.21
	3.3	Observed inappropriate affect	0	6	0.33	0.88
4. Negative Symptoms	4.1	Alogia	0	5	1.23	1.25
	4.2	Avolition/apathy	0	6	2.69	1.58
	4.3	Anhedonia	0	6	2.58	1.81
5. Behavioural Change	5.1	Social isolation	0	6	2.35	1.66
	5.2	Impaired role function	0	6	2.54	1.84
	5.3	Disorganizing/odd/stigmatising behaviour	0	5	0.56	1.07
	5.4	Aggression/dangerous behaviour	0	6	2.11	1.64
6. Motor/Physical Changes	6.1	Subjective complaints of impaired motor functioning	0	4	0.51	0.92
	6.2	Informant reported or observed changes in motor functioning	0	4	0.12	0.48
	6.3	Subjective complaints of impaired bodily sensation	0	6	0.64	1.28
	6.4	Subjective complaints of impaired autonomic functioning	0	5	0.85	1.37
7. General Psychopathology	7.1	Mania	0	6	0.68	1.29
	7.2	Depression	0	6	2.99	1.43
	7.3	Suicidality and self-harm	0	6	1.68	1.60
	7.4	Mood swings/lability	0	5	1.42	1.52
	7.5	Anxiety	0	6	2.79	1.62
	7.6	Obsessive compulsive symptoms	0	6	1.19	1.62
	7.7	Dissociative symptoms	0	6	1.06	1.53
	7.8	Impaired tolerance to normal stress	0	5	1.90	1.78

2.3.3 Test of normality

CAARMS scores for each item were examined for any significant variation from normal distribution by looking at individual histograms for each item (Appendix 2). Normal distribution is not a pre-requisite for factor analysis, however as some items varied from normal distribution, Principle Axis Factoring was used as the extraction method, which is less sensitive to normality than Maximum Likelihood.

2.3.4 Exploratory Factor Analysis

Exploratory factor analysis was conducted using SPSS (version 23) on the severity scores of all items, and factors were subjected to an oblique rotation – promax, to allow for correlation between factors. Only loadings greater than 0.4 were used to determine dimensions (Comrey, 1973).

The Keiser- Mayer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity showed the data's suitability for factor analysis. KMO = 0.891 (above the recommended value of 0.6) and Bartlett's test of sphericity was significant (χ^2 = 1482.4, df = 351, p<0.00). The data had a high level of internal consistency, as determined by a Cronbach's alpha of 0.821.

Examination of the output showed that the removal of 3 items would result in an increase in Cronbach's alpha: 3.2 - Observed Blunted affect, 7.1 – Mania and 7.6 – Obsessive Compulsive symptoms. These three also had low Corrected Item-Total Correlation, which would indicate they may need to be removed. The results are shown in the table 4 below.

Table 4: Internal Consistency Statistics for all CAARMS Items

Number	CAARMS Item	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Squared Multiple Correlation	Cronbach's Alpha if Item Deleted
1.1	Unusual thought content and non-bizarre ideas	40.33	253.173	0.270	0.196	0.818
1.2	Perceptual abnormalities	40.17	250.388	0.258	0.171	0.820
1.3	Disorganized speech	41.41	253.696	0.272	0.290	0.818
2.1	Subjective cognitive change	40.75	245.506	0.544	0.381	0.808
2.2	Observed cognitive change	42.29	261.294	0.194	0.265	0.820
3.1	Subjective emotional disturbance	41.10	242.264	0.503	0.349	0.808
3.2	Observed blunted affect	42.66	264.900	0.103	0.230	**0.822
3.3	Observed inappropriate affect	42.11	260.206	0.178	0.296	0.821
4.1	Alogia	41.76	248.642	0.465	0.367	0.811
4.2	Avolition/apathy	40.30	238.378	0.570	0.523	0.805
4.3	Anhedonia	40.41	232.992	0.584	0.627	0.803
5.1	Social isolation	40.64	237.456	0.555	0.449	0.805
5.2	Impaired role function	40.45	237.337	0.491	0.404	0.808
5.3	Disorganizing/odd/stigmatising behaviour	42.43	257.185	0.301	0.262	0.817
5.4	Aggression/dangerous behaviour	40.88	246.034	0.385	0.347	0.813
6.1	Subjective complaints of impaired motor functioning	42.48	259.139	0.293	0.235	0.817
6.2	Informant reported or observed changes in motor functioning	42.87	264.930	0.219	0.278	0.820
6.3	Subjective complaints of impaired bodily sensation	42.35	258.669	0.202	0.182	0.820
6.4	Subjective complaints of impaired autonomic functioning	42.14	254.657	0.277	0.184	0.818
7.1	Mania	42.31	264.465	**0.059**	0.188	**0.825
7.2	Depression	40.00	242.550	0.538	0.583	0.807
7.3	Suicidality and self-harm	41.31	246.226	0.396	0.369	0.813
7.4	Mood swings/lability	41.57	250.367	0.331	0.299	0.816
7.5	Anxiety	40.20	246.937	0.374	0.283	0.814
7.6	Obsessive compulsive symptoms	41.80	257.587	**0.162**	0.160	**0.823
7.7	Dissociative symptoms	41.93	255.318	0.224	0.164	0.820
7.8	Impaired tolerance to normal stress	41.09	241.493	0.432	0.285	0.811

** Indicates scores resulting in an increase above Cronbach's Alpha for *all* items of 0.821

Exploratory factor analysis was then conducted using Principal Axis Factoring (PAF) and promax rotation was applied to allow for correlation between the latent constructs. Initial EFA based on Eigen values showed 7 factors, accounting for 49% of the variance, however the scree plot (shown below in figure 3) indicated a clear break at 5 factors.

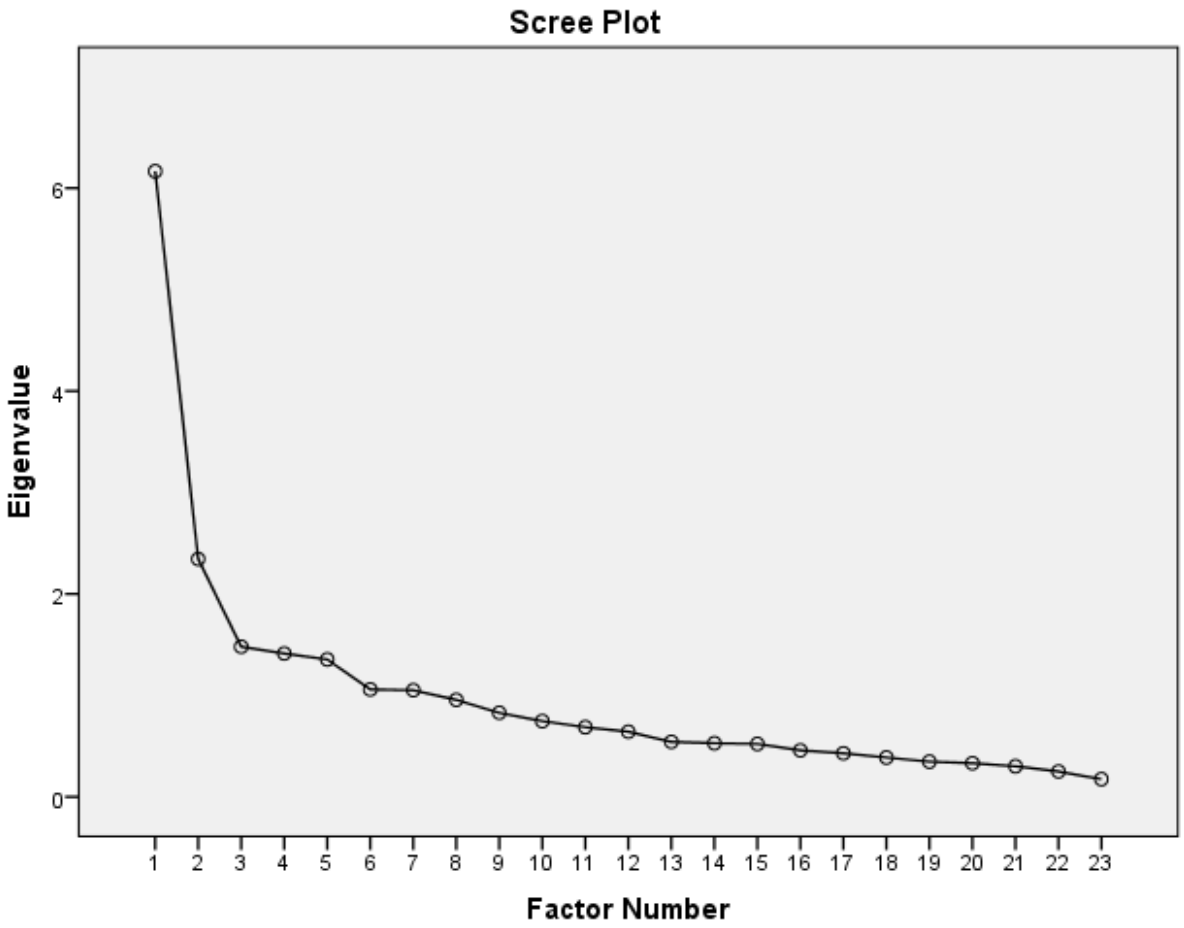

Figure 3: Scree plot of Principle Axis Factoring of all CAARMS Items with Promax Rotation based on Eigen Values

The communality for a given variable can be interpreted as the proportion of variation in that variable explained by the factors. A low communality of below 0.3 indicates that the item does not share any common variance and should not be included in the analysis. Communalities (shown in table 5 below) of three items (1.1 – Unusual Thought Content and Bizarre Ideas, 1.2 – Perceptual Abnormalities and 7.7 – Dissociative

Symptoms) were under the recommended value of 0.3 (Child, 1990), and were therefore excluded from the factor analysis.

Table 5: Communalities of all CAARMS Items

CAARMS group	Number	CAARMS Item	Extraction
1. Positive Symptoms	1.1	Unusual thought content and non-bizarre ideas	**0.247
	1.2	perceptual abnormalities	**0.262
	1.3	Disorganized speech	0.512
2. Cognitive Change	2.1	Subjective cognitive change	0.546
	2.2	Observed cognitive change	0.309
3. Emotional Disturbance	3.1	Subjective emotional disturbance	0.475
	3.2	Observed blunter affect	0.511
	3.3	Observed inappropriate affect	0.316
4. Negative Symptoms	4.1	Alogia	0.601
	4.2	Avolition/apathy	0.663
	4.3	Anhedonia	0.814
5. Behavioural Change	5.1	Social isolation	0.517
	5.2	Impaired role function	0.450
	5.3	Disorganizing/odd/stigmatising behaviour	0.360
	5.4	Aggression/dangerous behaviour	0.613
6. Motor/Physical Changes	6.1	Subjective complaints of impaired motor functioning	0.384
	6.2	Informant reported or observed changes in motor functioning	0.509
	6.3	Subjective complaints of impaired bodily sensation	0.689
	6.4	Subjective complaints of impaired autonomic functioning	0.394
7. General Psychopathology	7.1	Mania	0.369
	7.2	Depression	0.762
	7.3	Suicidality and self-harm	0.494
	7.4	Mood swings/lability	0.430
	7.5	Anxiety	0.525
	7.6	Obsessive compulsive symptoms	0.358
	7.7	Dissociative symptoms	**0.299
	7.8	Impaired tolerance to normal stress	0.423

** Indicates scores below recommended cut off of 0.3

A further two items were subsequently eliminated (6.3 – Subjective Complaints of Bodily Sensation and 6.4 - Subjective complaints of impaired autonomic functioning) as they did not contribute to a simple factor structure and failed to meet a minimum criteria of having a primary factor loading of 0.4 or above, and no cross-loading of 0.3 or above.

Principle Axis Factor Analysis of the remaining 19 items revealed a 5-factor structure, accounting for 40% of the variance. Factor loadings are shown in table 6, cross loadings greater than 0.3 are shown and a graphic representation of this factor structure for comparison to figures 2 and 3 is shown in figure 4.

Table 6: Factor Loadings based on a Principle Axis Factoring with Promax rotation of 19 CAARMS Items

CAARMS Item	Factor				
4.3 ANHEDONIA	0.971				
4.2 AVOLITION/APATHY	0.819				
7.2 DEPRESSION	0.676				
3.1 SUBJECTIVE EMOTIONAL DISTURBANCE	0.496				
5.3 DISORGANISING/ODD/STIGMATISING BEHAVIOUR		0.765			
6.2 INFORMANT REPORTED OR OBSERVED CHANGES IN MOTOR FUNCTIONING		0.446			
6.1 SUBJECTIVE COMPLAINTS OF IMPAIRED MOTOR FUNCTIONING		0.406			
3.3 OBSERVED INAPPROPRIATE AFFECT		0.404			
1.3 DISORGANISED SPEECH			0.682		
4.1 ALOGIA			0.595		
2.2 OBSERVED COGNITIVE CHANGE			0.426		
2.1 SUBJECTIVE COGNITIVE CHANGE			0.405		
7.5 ANXIETY				0.620	
5.1 SOCIAL ISOLATION				0.478	
7.8 IMPAIRED TOLERANCE TO NORMAL STRESS				0.424	
5.2 IMPAIRED ROLE FUNCTION	0.338			0.407	
7.4 MOOD SWINGS/LABILITY					0.617
5.4 AGGRESSION/DANGEROUS BEHAVIOUR					0.432
7.3 SUICIDALITY AND SELF HARM	0.336				0.459

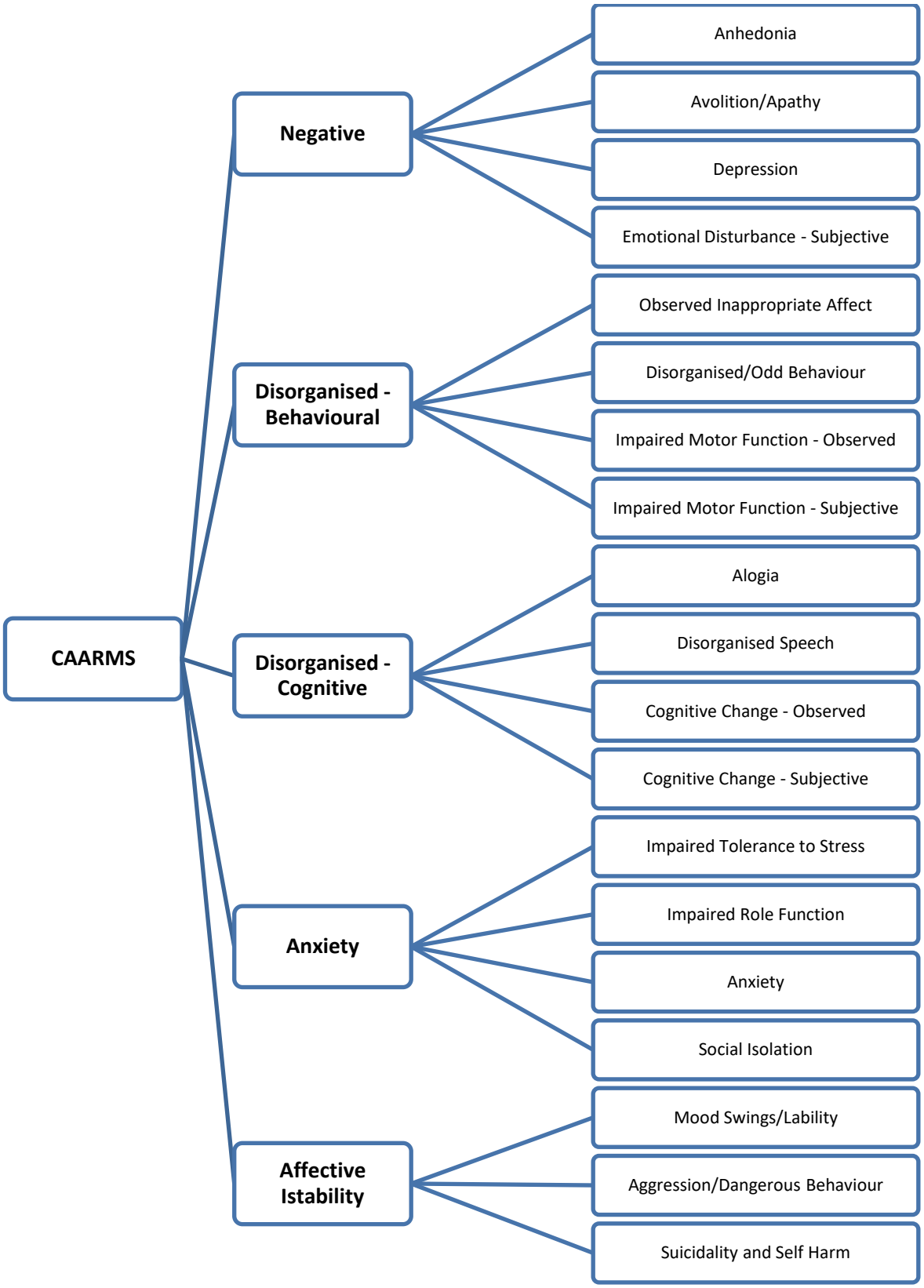

Figure 4: Factor structure found through principle axis factoring of UK CAARMS data (CAARMS 5)

The Excluded Items were:

- 1.1 UNUSUAL THOUGHT CONTENT AND NON BIZARRE IDEAS
- 1.2 PERCEPTUAL ABNORMALITIES
- 3.2 OBSERVED BLUNTER AFFECT
- 6.3 SUBJECTIVE COMPLAINTS OF IMPAIRED BODILY SENSATION
- 6.4 SUBJECTIVE COMPLAINTS OF IMPAIRED AUTONOMIC FUNCTIONING
- 7.1 MANIA
- 7.6 OCD SYMPTOMS
- 7.7 DISSOCIATIVE SYMPTOMS

2.3.5 Descriptive Statistics of Factor Scores

Items loading on the Negative factor were reported most frequently (97% of cases), whereas items loading on the Disorganised - Behavioural factor were reported the least (46% of cases). Composite scores were then created for each of the five factors, based on the mean of the items which had their primary loadings on each factor. Negative and Anxiety factors had the highest severity ratings and skewness and kurtosis were within the range for assuming normal distribution for Negative, Affective Instability, Anxiety and Disorganised - Cognitive factors, (descriptive statistics are shown in table 7 below). However, the Disorganised - Behavioural factor was positively skewed. Histograms are shown in Appendix 3.

As expected, all factors were highly correlated, with the exception of the Affective Instability and Disorganised – Behavioural factors. Correlations are shown in table 8 below.

Table 7: Descriptive Statistics of Composite Factor Scores

Factor	Minimum	Maximum	Mean	Std. Deviation	Skewness		Kurtosis		Percentage of Cases Reporting
	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic	Std. Error	
Negative	*0.000*	*5.500*	*2.536*	*1.254*	*-0.130*	*0.114*	*-0.744*	*0.227*	*97%*
Disorganised - Behavioural	*0.000*	*4.000*	*0.380*	*0.559*	*2.107*	*0.114*	*6.250*	*0.227*	*46%*
Disorganised - Cognitive	*0.000*	*4.000*	*1.438*	*0.862*	*0.156*	*0.114*	*-0.735*	*0.227*	*92%*
Anxiety	*0.000*	*5.250*	*2.394*	*1.221*	*-0.182*	*0.114*	*-0.742*	*0.227*	*95%*
Affective Instability	*0.000*	*4.333*	*1.735*	*1.170*	*0.202*	*0.114*	*-0.759*	*0.227*	*85%*

Table 8: Correlations between Factors Determined by Exploratory Factor Analysis

		Negative	Disorganised - Behavioural	Disorganised - Cognitive	Anxiety	Affective Instability
Negative	Correlation Coefficient	1.000				
	Sig. (2-tailed)					
Disorganised - Behavioural	Correlation Coefficient	.191**	1.000			
	Sig. (2-tailed)	0.000				
Disorganised - Cognitive	Correlation Coefficient	.342**	.335**	1.000		
	Sig. (2-tailed)	0.000	0.000			
Anxiety	Correlation Coefficient	.585**	.259**	.340**	1.000	
	Sig. (2-tailed)	0.000	0.000	0.000		
Affective Instability	Correlation Coefficient	.463**	0.089	.249**	.394**	1.000
	Sig. (2-tailed)	0.000	0.057	0.000	0.000	

2.3.6 Confirmatory Factor Analysis

Confirmatory Factor Analysis (CFA) was then conducted on the other (Non-UK) half of the data, using AMOS (version 23) to measure the goodness-of-fit of the alternative models.

The indices used to determine goodness of fit were χ^2, Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), Standardised Root Mean Square Residual (SRMR) and the Root

Mean Square Error of Approximation (RMSEA). χ^2 should be close to 2, where 0 is a perfect fit, CFI and TLI should be above 0.90, where 1 is a perfect fit, SRMR should be below 0.08 and the RMSEA should be below 0.06 where 0 is a perfect fit (Schreiber et al., 2006).

The input matrix used was a variance-covariance matrix and maximum likelihood estimation method was chosen to calculate the fit indices, because this method is relatively insensitive to sample size, non-normality and model size.

The models tested were:

1. One factor model of all CAARMS Items (CAARMS1)
2. Three factor model from Raballo (2011) (Raballo3)
3. Five Factor Model from Demjaha et al. (2010) (Demjaha5)
4. Five factor model found through EFA of UK data from this study (CAARMS5)
5. Seven factor model of CAARMS categories (CAARMS7)

The five models and their item loadings are shown below in figures 5-9.

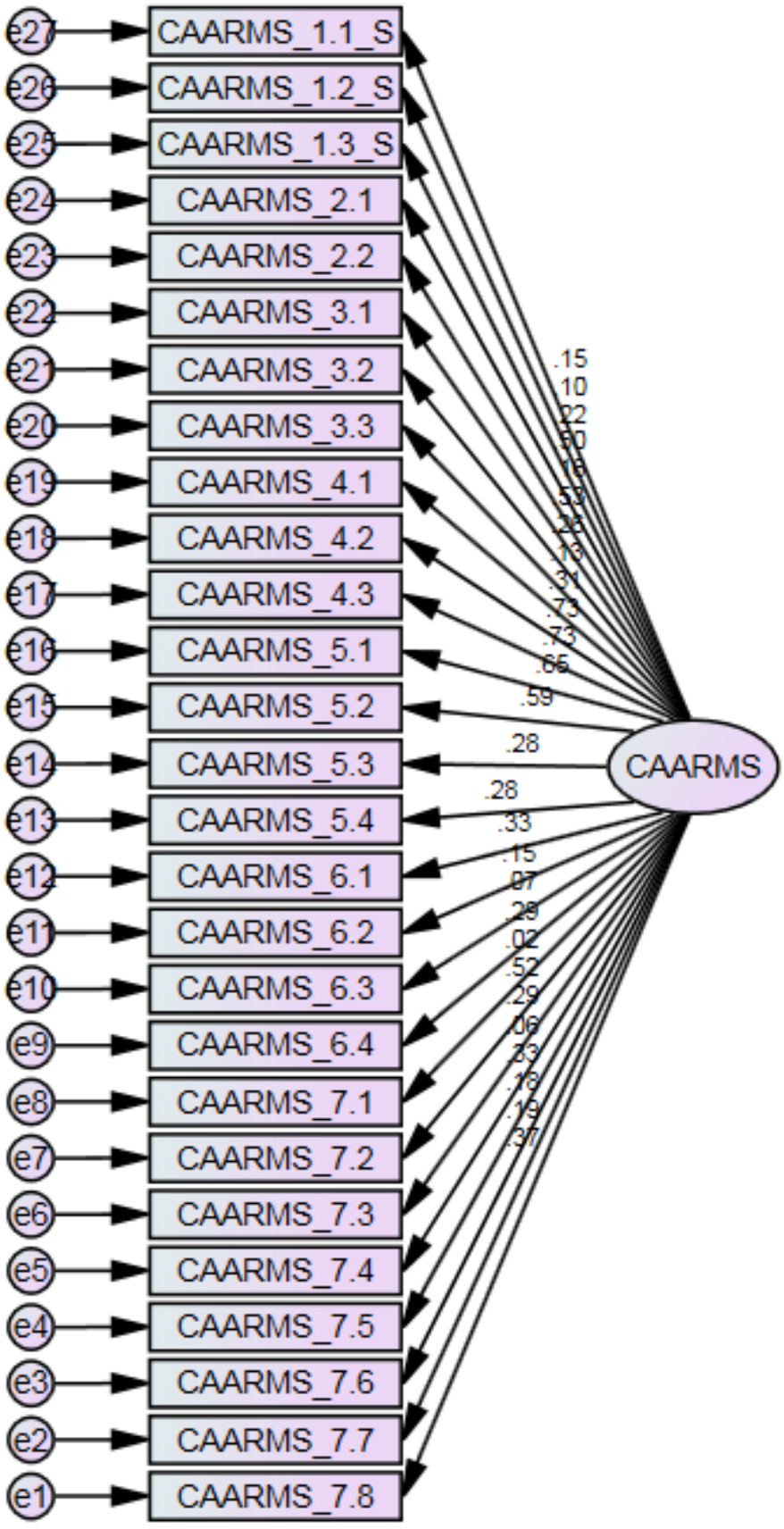

Figure 5: Standardised Regression Weights based on Confirmatory Factor Analysis of CAARMS 1 Factor Structure

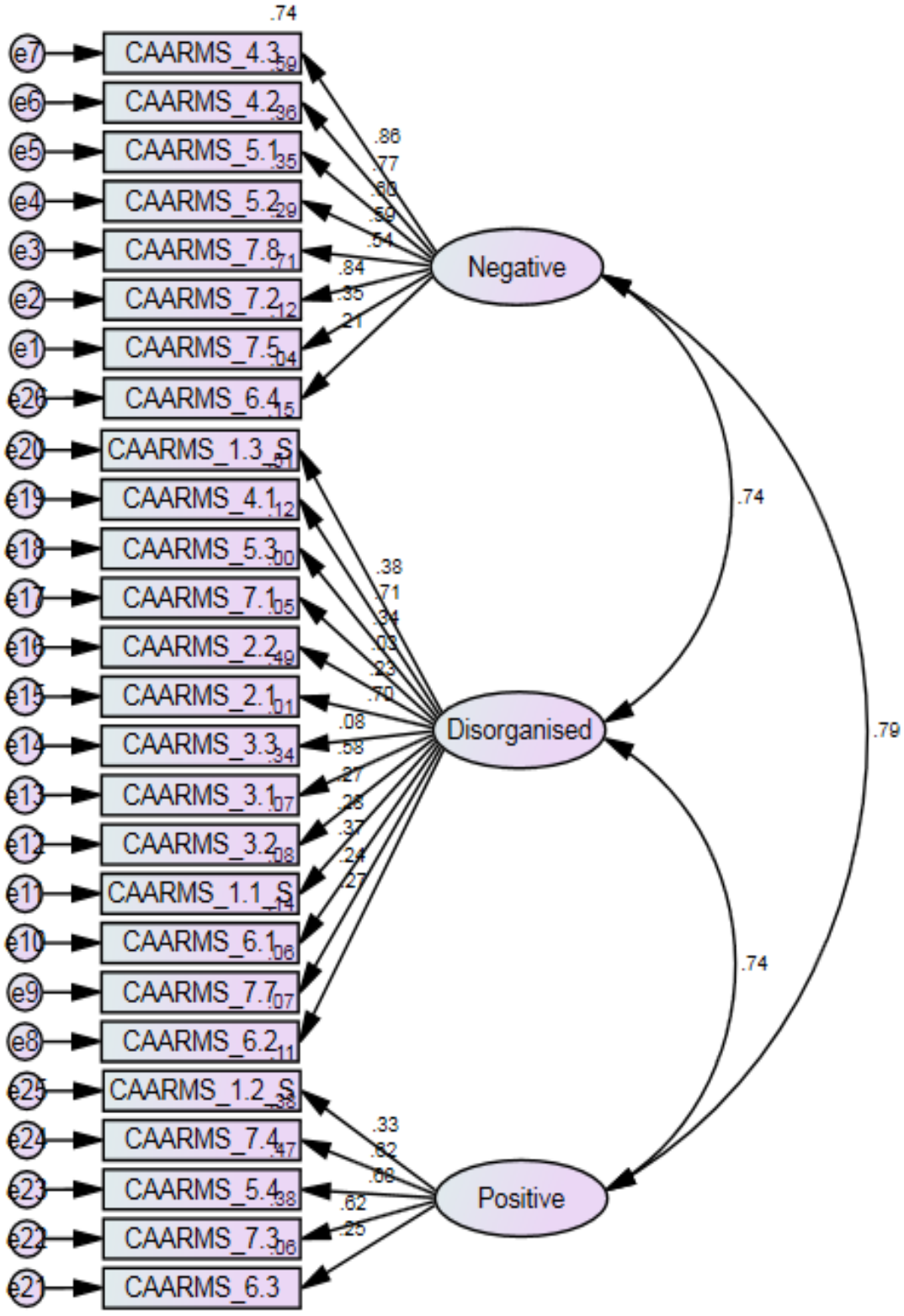

Figure 6: Standardised Regression Weights based on Confirmatory Factor Analysis of Raballo 3 Factor Structure

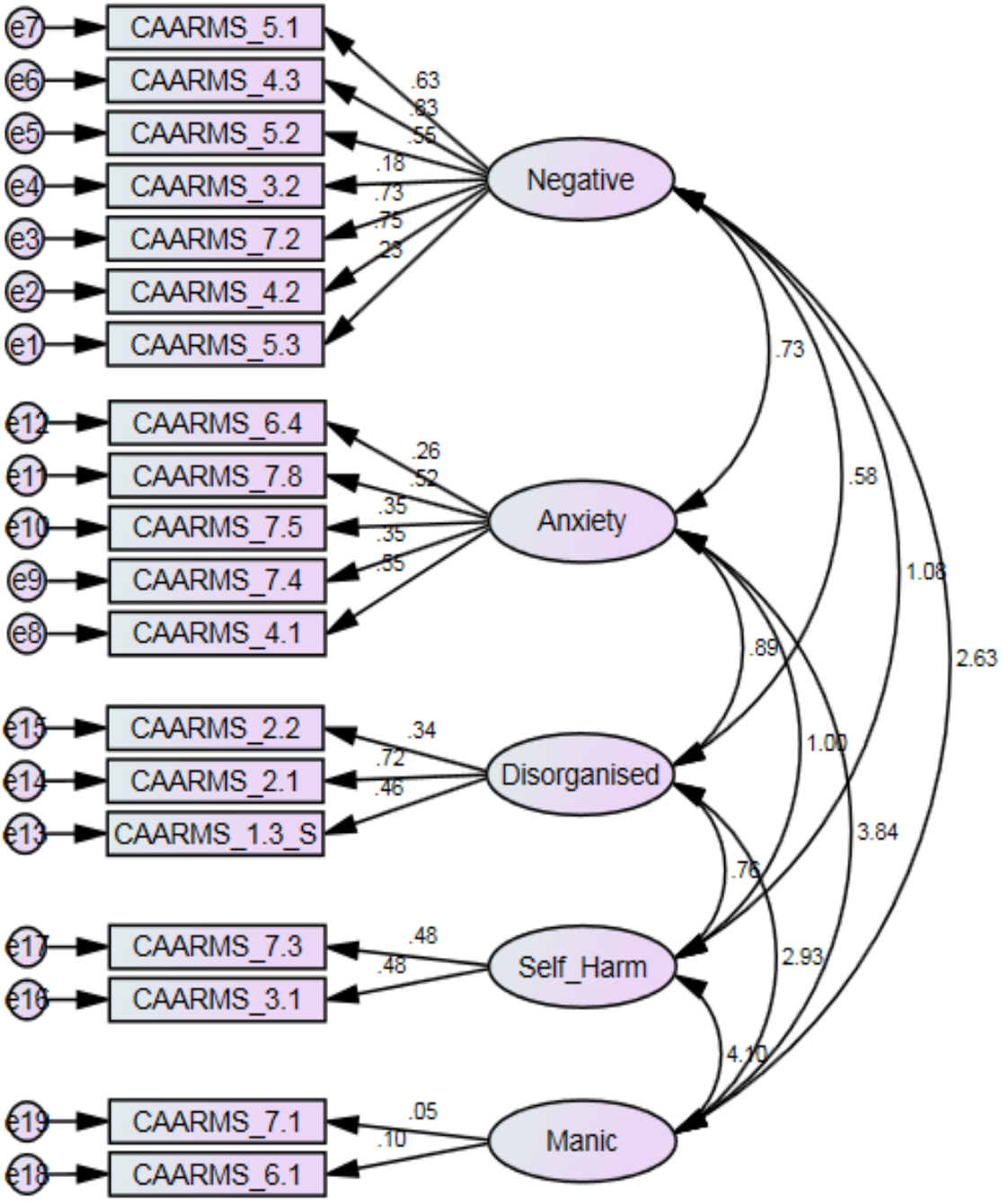

Figure 7: Standardised Regression Weights based on Confirmatory Factor Analysis of Demjaha 5 Factor Structure

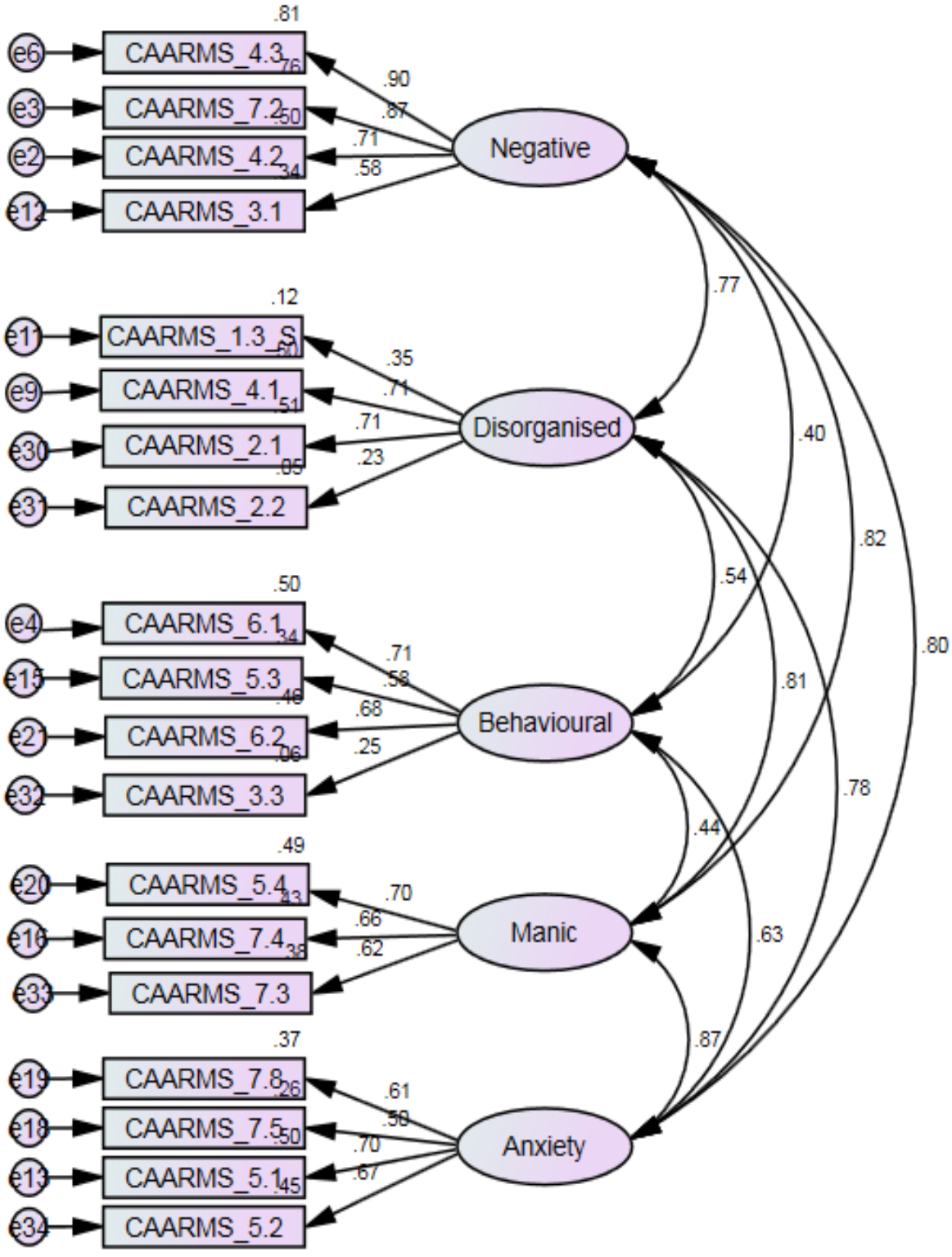

Figure 8: Standardised Regression Weights based on Confirmatory Factor Analysis of CAARMS 5 Factor Structure

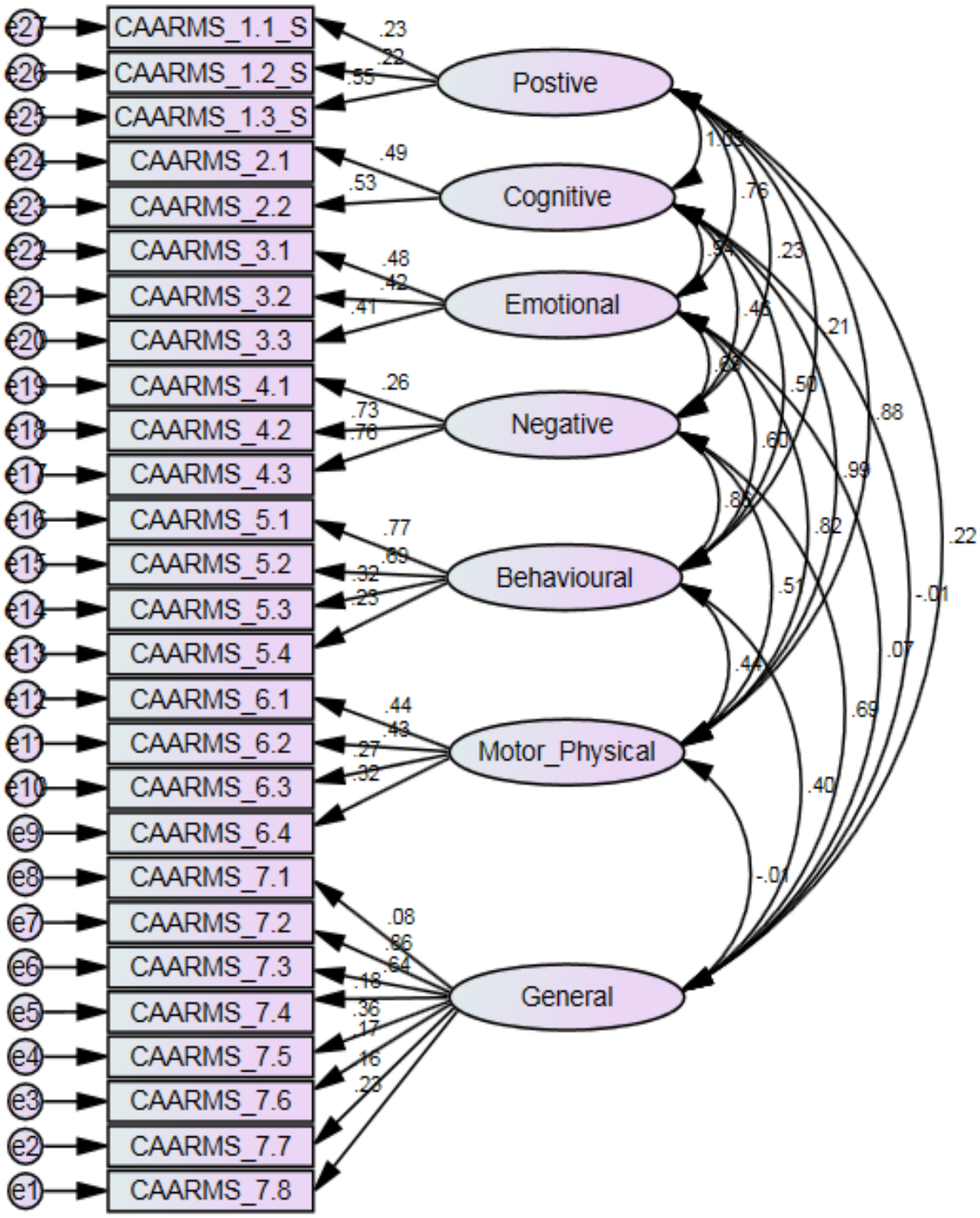

Figure 9: Standardised Regression Weights based on Confirmatory Factor Analysis of CAARMS 7 Factor Structure

The Goodness of Fit indices are shown below in table 9 for comparison.

Table 9: Comparative Goodness of Fit Indices for the 5 models tested using Confirmatory Factor Analysis

Model	χ^2	df	χ^2/df Cut off <2	CFI Cut off >0.95	TLI Cut off >0.95	SRMR Cut off <0.08	RMSEA Cut off <0.06
CAARMS 1	919	324	2.838	0.483	0.440	0.103	0.091
Raballo 3	924	296	3.122	0.660	0.627	0.094	0.095
Demjaha 5	921	142	6.483	0.759	0.710	0.961	0.088
CAARMS 5	187	142	**1.317	**0.95	0.928	**0.065	**0.052
CAARMS 7	719	303	2.372	0.639	0.582	0.098	0.078

** indicates value meets cut off point

As can be seen in the table above, the 5 factor model found in the UK dataset met the criteria for goodness of fit for the Non-UK dataset for four of the six measures.

2.4 Discussion

2.4.1 Aims and results of the Study

The aim of this study was to investigate symptom dimensions in a large dataset collected from individuals who presented to clinical Ultra High Risk services, and then compare the fit of these dimensions with those previously identified in other datasets involving this population in a second dataset.

Exploratory Factor Analysis (EFA) of the UK data revealed a five factor structure, consisting of Negative, Disorganised - Behavioural, Disorganised - Cognitive, Anxiety and Affective Instability dimensions, each comprising three or more CAARMS items. There was good internal consistency, and this structure accounted for 40% of the total

variance. Confirmatory Factor Analysis (CFA) using the non-UK data to compare five theoretical structures (two described in the literature, one identified through EFA, and two using the CAARMS items as they are set out in the assessment instrument) showed that the five factor structure from the UK provided the best fit for the data, with goodness of fit indices CFI, SRMR, RMSEA, and χ^2/df meeting the generally used cut off points recommended by Hu and Bentler (1999). Although the TLI of 0.932 did not meet the 0.95 cut off point and chi squared was not significant: $\chi^2(142) = 184$, p=0.000, many investigators have argued against the use of chi-square as a test of goodness of fit, due to its dependency on sample size (Marsh et al., 1988), model size (Schreiber et al., 2006) and distribution of variables (Curran et al., 1996), and it has been suggested that a significant chi-square value is not an indication of poor fit (Schermelleh-Engel et al., 2003).

An important characteristic of any dimensional structure is that it must have face validity. Each of the factors in the structure that I have identified consists of psychopathological items that would be expected to cluster together, and each of the dimensions corresponds to a type of symptom that is prominent in UHR subjects. The structure is also in keeping with the factor structures that have previously been described in UHR subjects (Demjaha et al. (2010), and in first episode psychosis (Good et al., 2004; Peralta & Cuesta, 1999) and chronic schizophrenia (Dikeos et al., 2006; Drake et al., 2004; Lindenmayer et al., 1995a).

There was a predominant negative factor, which accounted for more variance than the other four factors combined. This finding is similar to that reported for the negative dimension described in both chronic and first episode studies (Fernández et al., 2006;

Liddle, 1987; Van Os et al., 2009). It has also been evident in UHR subjects, regardless of whether symptoms were assessed using the Scale of Prodromal Symptoms - SOPS (Fernández et al., 2006; Hawkins et al., 2004) or the CAARMS (Demjaha et al., 2010; Raballo, 2011), and irrespective of the particular factor structure found.

2.4.2 Comparison with Previous Studies

A five dimensional structure has been found in many other studies, in patients with psychosis (Dikeos et al., 2006; Drake et al., 2004; Good et al., 2004; Lindenmayer et al., 1995a; Lindenmayer et al., 1995b; Peralta & Cuesta, 1999) and in subjects at UHR for psychosis (Demjaha et al. (2010). The five factor structure identified in the present study does not exactly replicate Demjaha's, as demonstrated in the poor goodness of fit indices for that structure in the CFA. Nevertheless, three of the five factors comprised similar items: in both models, the Negative factor included Avolition, Anhedonia and Depression, the Disorganised factor included Observed Cognitive Change, Subjective Cognitive Change and Disorganised Speech, and the Anxiety factor included Anxiety and Impaired Tolerance to Normal Stress. There was also some consistency between the structure found here and the three factor Model described by Raballo et al (2011): again, in both models the Negative factor included Avolition, Anhedonia and Depression, and the Affective Instability factor included Mood Swings, Aggression and Suicidality. In addition, all items loading on the Disorganised - Behavioural and Disorganised - Cognitive factor in the present dataset were combined into one factor (the Disorganised factor) in the Raballo model. These similarities are shown in the Table 10 below.

Table 10: Comparison of Current and Previous CAARMS Models

Demjaha	CAARMS 5	Raballo
Negative	**Negative**	**Negative**
4.3 ANHEDONIA	4.3 ANHEDONIA	4.3 ANHEDONIA
4.2 AVOLITION/APATHY	4.2 AVOLITION/APATHY	4.2 AVOLITION/APATHY
7.2 DEPRESSION	7.2 DEPRESSION	7.2 DEPRESSION
3.2 OBSERVED BLUNTER AFFECT	3.1 SUBJECTIVE EMOTIONAL DISTURBANCE	5.2 IMPAIRED ROLE FUNCTION
5.2 IMPAIRED ROLE FUNCTION		7.8 IMPAIRED TOLERANCE TO NORMAL STRESS
5.1 SOCIAL ISOLATION		5.1 SOCIAL ISOLATION
5.3 DISORGANISING/ODD BEHAVIOUR		7.5 ANXIETY
		6.4 SUBJECTIVE AUTONOMIC FUNCTIONING
Disorganised	**Disorganised - Cognitive**	**Disorganised**
1.3 DISORGANISED SPEECH	1.3 DISORGANISED SPEECH	1.3 DISORGANISED SPEECH
2.2 OBSERVED COGNITIVE CHANGE	2.2 OBSERVED COGNITIVE CHANGE	2.2 OBSERVED COGNITIVE CHANGE
2.1 SUBJECTIVE COGNITIVE CHANGE	2.1 SUBJECTIVE COGNITIVE CHANGE	2.1 SUBJECTIVE COGNITIVE CHANGE
	4.1 ALOGIA	4.1 ALOGIA
		7.1 MANIA
Self-Harm	**Disorganised – Behavioural**	7.7 DISSOCIATIVE SYMPTOMS
7.3 SUICIDALITY AND SELF HARM	5.3 DISORGANISING/ODD BEHAVIOUR	5.3 DISORGANISING/ODD BEHAVIOUR
3.1 SUBJECTIVE EMOTIONAL DISTURBANCE	6.2 INFORMANT REPORTED OR OBSERVED CHANGES IN MOTOR FUNCTIONING	6.2 INFORMANT REPORTED OR OBSERVED CHANGES IN MOTOR FUNCTIONING
	6.1 SUBJECTIVE COMPLAINTS OF IMPAIRED MOTOR FUNCTIONING	6.1 SUBJECTIVE COMPLAINTS OF IMPAIRED MOTOR FUNCTIONING
	3.3 OBSERVED INAPPROPRIATE AFFECT	3.3 OBSERVED INAPPROPRIATE AFFECT

Demjaha	CAARMS 5	Raballo
		3.2 OBSERVED BLUNTER AFFECT
		3.1 SUBJECTIVE EMOTIONAL DISTURBANCE
		1.1 UNUSUAL THOUGHT CONTENT AND NON BIZARRE IDEAS
Manic	**Affective Instability**	**Positive**
7.1 MANIA	7.4 MOOD SWINGS/LABILITY	7.4 MOOD SWINGS/LABILITY
6.1 SUBJECTIVE COMPLAINTS OF IMPAIRED MOTOR FUNCTIONING	5.4 AGGRESSION/DANGEROUS BEHAVIOUR	5.4 AGGRESSION/DANGEROUS BEHAVIOUR
	7.3 SUICIDALITY AND SELF HARM	7.3 SUICIDALITY AND SELF HARM
		6.3 SUBJECTIVE COMPLAINTS OF IMPAIRED BODILY SENSATION
		1.2 PERCEPTUAL ABNORMALITIES
Anxiety	**Anxiety**	
7.5 ANXIETY	7.5 ANXIETY	
7.8 IMPAIRED TOLERANCE TO NORMAL STRESS	7.8 IMPAIRED TOLERANCE TO NORMAL STRESS	
7.4 MOOD SWINGS/LABILITY	5.1 SOCIAL ISOLATION	
4.1 ALOGIA	5.2 IMPAIRED ROLE FUNCTION	

Demjaha	CAARMS 5	Raballo
EXCLUDED:	**EXCLUDED:**	**EXCLUDED:**
7.6 OCD SYMPTOMS	7.6 OCD SYMPTOMS	7.6 OCD SYMPTOMS
1.1 UNUSUAL THOUGHT CONTENT AND NON BIZARRE IDEAS	1.1 UNUSUAL THOUGHT CONTENT AND NON BIZARRE IDEAS	
1.2 PERCEPTUAL ABNORMALITIES	1.2 PERCEPTUAL ABNORMALITIES	
6.3 SUBJECTIVE COMPLAINTS OF IMPAIRED BODILY SENSATION	6.3 SUBJECTIVE COMPLAINTS OF IMPAIRED BODILY SENSATION	
7.7 DISSOCIATIVE SYMPTOMS	7.7 DISSOCIATIVE SYMPTOMS	
5.4 AGGRESSION/DANGEROUS BEHAVIOUR	3.2 OBSERVED BLUNTER AFFECT	
3.3 OBSERVED INAPPROPRIATE AFFECT	7.1 MANIA	
6.2 INFORMANT REPORTED OR OBSERVED CHANGES IN MOTOR FUNCTIONING	6.4 SUBJECTIVE COMPLAINTS OF IMPAIRED AUTONOMIC FUNCTIONING	

The most notable similarity across all of the three CAARMS models, and the SOPS (Fernández et al., 2006; Hawkins et al., 2004) model, is that a negative factor was predominant. In all of these models, this factor accounted for the most variance, consistent with findings in first episode and chronic patients (Dikeos et al., 2006; Liddle, 1987; Lindenmayer et al., 1995a). This is also the case with the Disorganised factor, which, although it accounts for less variance, is consistently reported across all UHR models.

A notable difference between this and other models is the absence of a positive psychotic factor. Hawkins et al. (2004) described an "unusual thought content-perceptual abnormalities" factor in a study of SOPS data from 94 UHR subjects, while Fernández et al. (2006) found an "unusual thought content-suspiciousness" factor in 30 patients. In the present study, Perceptual Abnormalities and Unusual Thought Content were excluded from the EFA because of low Communalities. This is in keeping with the Demjaha et al. (2010), who also failed to identify a positive symptom dimension, suggesting that this may be due to differences between the CAARMS and SOPS scales. Five of 19 SOPS items, as opposed to 3 of 27 CAARMS items relate to positive symptoms. Furthermore, with the CAARMS, inclusion as an UHR subject (via the Attenuated Psychotic Symptoms criteria) requires a score of 3 or more on one of the positive symptom items. In the UK, the majority of UHR subjects meet the Attenuated Symptoms criteria (86%) and have relatively high positive symptom scores. As a result, the variance associated with these items within the UHR sample may have been too small to allow clear distinction of a positive factor.

2.4.3 Limitations

The present study used a similar sampling method to both those by Demjaha et al. (2010) and Raballo (2011), with recruitment of UHR subjects who had been referred to a specialised mental health service from defined local catchment area populations. The UK data set used in the EFA had exactly the same referral and recruitment pathway as in the study by Demjaha et al. (2010), and a proportion of the Non-UK sample (6.4%) used the same referral and recruitment pathway as Raballo (2011). However, despite these similarities there may still be sampling inconsistencies. Although the appropriate statistical tests were performed to ensure the statistical validity of combining the datasets, the UK sample was a combination of data collected from two different studies, over a period of 6 years. This was also the case with the non-UK data, with all the data collected as part of one overarching study over 5 years, but at different sites and by different researchers.

The sample size was over double that in any previous study of symptom dimensions in UHR subjects (94 (Hawkins et al., 2004), 30 (Lemos et al., 2006), 122 (Demjaha et al., 2010), 223 (Raballo et al., 2011) and 461 in this study), and met minimum sample size requirements in statistical terms (MacCallum et al., 1999). Nevertheless, ideally factor analyses require even larger datasets, and there is good evidence that the goodness of fit indices in CFA depend on the sample size (Marsh et al., 1988). Unlike many test statistics, the goodness of fit indices used in CFA do not have corresponding p-values, but use a set cut-off point to determine acceptance of the model. This cut-off point for relative fit indices has been

disputed and was previously 0.9, but Hu and Bentler (1999) have recommended a more stringent cut-off point of 0.95. Although this value is still widely used, an even more stringent cut-off of 0.97 has been proposed (Schermelleh-Engel et al., 2003), and some investigators have suggested that cut-offs should be abandoned altogether (Barrett, 2007). There have also been debates about the usefulness of the chi-square statistic, due to the limitations listed above, and there is disagreement as to whether, as suggested by Schermelleh-Engel et al. (2003), it is valid to accept a model despite a significant result (Barrett, 2007).

In the present study, discrepancies in agreement over model fit indices have been addressed by including a range of statistics that have been shown to perform well with respect to sample size and model mis-specification, and that are appropriate for the sample size and type of data used here. Nevertheless, the inadequacy of these indices remains a topic of debate (Lance et al., 2016; Markland, 2007; Marsh et al., 2004).

In spite of these limitations, the data indicate that the symptoms of the UHR state load onto five different dimensions, corresponding to Negative, Disorganised, Cognitive, Anxiety and Mania symptoms.

2.4.4 Future Research Directions

Dimensions provide a useful means of characterising and understanding symptomatology in psychosis. However, in UHR subjects, baseline symptom dimensions may be of particular interest in relation to other clinical and biological measures, and to long term clinical outcomes.

The following chapters will look at how the five symptom dimensions found here relate to neurobiological correlates, to clinical variables in UHR subjects at presentation and to their clinical outcomes at follow up.

3 Neurobiological Correlates of Symptom Dimensions

3.1 Introduction

3.1.1 Resting Cerebral Blood Flow (rCBF)

Brain function relies on aerobic metabolism, for which a consistent oxygenated blood supply is essential. In response to neural activity nearby vessels dilate, substantially increasing CBF. The phenomenon that links neural activity to a proportionate increase in CBF is termed Neurovascular coupling (NVC). We can therefore measure regional cerebral blood flow (CBF) to provide a direct and quantitative measure of perfusion and an indirect measure of neural function through NVC (Huneau et al., 2015). CBF can therefore be used to examine the level and location of neural activity in the human brain in vivo (Phillips et al., 2016).

In the 1940's, Kety et al. (1948) applied a nitrous oxide inhalation method to study CBF in 30 subjects with schizophrenia and 35 controls. Their study did not show a difference between patients and controls, or between patients split by acute and chronic presentation. However, they proposed that as their method obtains only a mean value for the whole brain, their finding does not rule out the possibility of regional changes. Kety proposed that as schizophrenia is characterized by specific symptoms, rather than a global impairment of function, abnormalities of perfusion in schizophrenia may only be apparent when examining regional, not global, activity.

Since the development and wide usage of the nitrous oxide technique in the 1950s and 1960s, several technical advances to measure CBF have been developed. These will be discussed in the following sections.

3.1.2 Measuring Cerebral Blood Flow

1. *Positron Emission Tomography (PET)* – PET is a versatile imaging modality that provides dynamic information regarding the metabolism and physiology of the brain. Intravenous injection of positron-emitting radionuclides allows a visualization of the blood flow in the brain and provides quantitative information regarding the function. Initial investigations in to CBF and symptoms in schizophrenia by P. F. Liddle et al. (1992) used PET to measure resting CBF and found distinct patterns of CBF according to symptom type. However, a consideration for PET imaging studies is that they involve the injection of radioactive tracers, and require a cyclotron to produce the tracer, making them expensive and logistically difficult.
2. *Single Photon Emission Computed Tomography (SPECT)* – similarly to PET, SPECT produces tomographic images of the distribution of radioactivity in the body. The uptake within the brain remains constant for several hours and is proportional to the cerebral blood flow. Unlike PET, SPECT measures flow, but not regional metabolism. It produces non-quantitative results and the imaging resolution is not as high as that of PET. SPECT was used by many studies in the 1990's to measure CBF in schizophrenia finding distinct patterns of CBF according to positive or negative symptom divisions (Erkwoh et al., 1999; Lewis et al., 1992; Min et al., 1999; Sabri et al., 1997).

However, again it relies on intravenous injection and radioactive production.

3. *Arterial spin labelling (ASL)* - More recently, rCBF has been examined using perfusion MRI - a technique that allows for quantitative measurement of CBF by using magnetically labelled arterial blood water as an endogenous tracer (Detre et al., 1992). Despite the value of PET and SPECT in informing the neurobiology of schizophrenia, both are limited by invasiveness, reliance on radioactive tracer material, and expense. These limitations make PET and SPECT imaging difficult to implement in large-scale, multi-site studies. In contrast, the non-invasive nature of ASL, conducted using an MRI scanner, allows for repeated measurements with limited discomfort to participants. ASL provides quantitative measurement of CBF which has been shown to be stable, reliable and similar to PET/SPECT (Chen et al., 2008; Gevers et al., 2009; Wang et al., 2011).

3.1.3 Cerebral Blood Flow in Psychosis

Finding a unifying concept to account for the diversity of psychopathology in schizophrenia is a central challenge to contemporary research. One area in which extensive research has been conducted is in examining underlying neurobiology. The heterogeneity in symptom presentation and the wide range of courses and outcomes in schizophrenia however, mean that the search for neural substrates has been a complex process.

After Ingvar and Franzén (1974) first described abnormal blood flow in frontal and temporal regions in patients with schizophrenia compared to controls, decreased

CBF in frontal and temporal regions was reported in many studies using either PET or SPECT (Andreasen et al., 1992; Buchsbaum et al., 1982; Ebmeier et al., 1993; Erkwoh et al., 1999; Tamminga et al., 1992), and hypofrontality was considered a key pathophysiological finding in schizophrenia (Ebmeier et al., 1993). However, some subsequent findings were contradictory (Catafau et al., 1994; Cleghorn et al., 1989; Volkow et al., 1987), leading to questions about the robustness of this finding (Gur & Gur, 1995). The inconsistency of this finding has been attributed to many factors including: duration of illness, medication status and methods of brain imaging.

More recently, several studies have used ASL to examine CBF in schizophrenia. Horn et al. (2009) found no group differences in CBF between patients and healthy controls but found a positive correlation between severity of thought disorder and increased blood flow in left inferior frontal gyrus (pars orbitalis), left posterior superior temporal gyrus /angular gyrus and the left anterior insula. Scheef et al. (2010) found patients had areas of hypoperfusion in bilateral frontal and parietal lobes and middle and anterior cingulate gyrus, but hyperperfusion in cerebellum, brainstem, and thalamus compared to controls. Both of these studies were in small sample sizes (n=13 and n=11 respectively), however two more recent studies, in larger sample sizes found an overall pattern of prefrontal hypoperfusion and subcortical/temporal hyperperfusion: Pinkham et al. (2011) found patients showed increased CBF in left putamen/superior corona radiata and right middle temporal gyrus in a sample of 40 patients, and Zhu et al. (2015) found increased CBF in the bilateral inferior temporal gyri, thalami and putamen and

decreased CBF in the left insula and middle frontal gyrus and the bilateral anterior cingulate cortices and middle occipital gyri in a sample of 100 subjects. Both of these studies also investigated the correlation of CBF with anti-psychotic medication finding a positive dose-dependent response in left putamen and right middle temporal gyrus (respectively).

3.1.4 Cerebral Blood flow and Symptoms of Psychosis

Through refining analyses to look at groups of presenting symptoms, rather than all symptoms combined under the diagnostic category of schizophrenia, researchers may be able to provide a heuristic theoretical framework to better explore aetiology and clinical course to inform intervention, or enable prevention.

This concept was initially explored by P. F. Liddle et al. (1992), who argued that the clinical heterogeneity of schizophrenia is likely to reflect heterogeneity in the underlying neuropathology. Liddle had previously shown using PCA that the psychotic symptoms of schizophrenia loaded on to three different psychopathological dimensions (Liddle, 1987; Liddle & Barnes, 1990):

1. 'Positive' (reality distortion, delusions and hallucinations)
2. 'Negative' (poverty of speech, flatness of affect and decreased spontaneous movement)
3. 'Disorganised' (disorders of the form of thought and inappropriate affect)

Using Positron Emission Tomography (PET), Liddle and his colleagues examined regional Cerebral Blood Flow (CBF), and found that each symptom dimension was

associated with a particular topographical pattern of CBF, the results from this study are shown in table 11 below.

Table 11: Results from 1992 Liddle study - correlation coefficients of rCBF and dimension scores

Region	Coordinates			Negative Dimension	Disorganised Dimension	Positive Dimension
	x	y	z			
Right caudate	20	16	12	0.55		
Left caudate	-22	10	4	0.52		
Left dorsolateral prefrontal cortex	-26	54	8	-0.46		
Left superior parietal association cortex	-50	-44	32	-0.52		
right anterior cingulate	8	30	16		0.54	
Mediodorsal thalamus	2	-20	4		0.43	
Right ventrolateral prefrontal cortex	26	32	0		-0.46	
Right angular gyrus	42	-60	8		-0.48	
Left angular gyrus	-40	-74	16		-0.45	
Left parahippocampal gyrus	-12	-28	-4			0.46
Left ventral striatum	-16	4	-4			0.43
Right posterior cingulate	10	-58	28			-0.53

Additionally, the brain regions associated with each dimension were consistent with those predicted on the basis of behavioural and neuropsychological features characteristic of each syndrome. For example, the negative syndrome was linked to hypoperfusion of the prefrontal cortex and striatum, as shown in table 11.

Subsequent studies using PET and SPECT examining the correlates of symptom dimensions have further clarified the relationships between symptomatology and regional hyper- and hypoperfusion at rest: negative symptoms have been associated with reduced CBF in frontal (Erkwoh et al., 1999; Lewis et al., 1992;

Sabri et al., 1997), temporal (Esel et al., 2000; Sabri et al., 1997) and thalamic regions (Min et al., 1999; Sabri et al., 1997), and positive symptoms have been associated with increased CBF in temporal (Esel et al., 2000; Kohno et al., 2006; Mathew et al., 1988; Parellada et al., 1998), parietal (Erkwoh et al., 1999; Esel et al., 2000; Franck et al., 2002; Mathew et al., 1988) and frontal regions (Erkwoh et al., 1999), and decreased CBF in posterior cingulate gyrus and lingual gyrus (Franck et al., 2002; Sabri et al., 1997). Notably, when scans were carried out on participants in both florid and remitted states, Erkwoh et al. (1999) and Sabri et al. (1997) both found correlations with increased CBF present in a florid state were no longer present after remission or neuroleptic treatment.

All the studies mentioned above used PET/SPECT. The only study to date to use ASL to examine CBF using a dimensional approach was by Pinkham et al. (2011), who used ASL to distinguish differences in CBF associated with positive and negative symptoms. Severity of negative symptoms was associated with reduced CBF in bilateral superior temporal gyrus, cingulate gyrus, and left middle frontal gyrus, while severity of positive symptoms was related to both higher CBF in cingulate gyrus and superior frontal gyrus and decreased CBF in precentral gyrus/middle frontal gyrus.

Understanding the pathophysiology of different symptoms may provide a rational basis for the development of novel treatments for specific psychotic symptoms. This is particularly relevant for negative symptoms, for which there are still no effective treatments (Fusar-Poli et al., 2015)

3.1.5 Neurobiological Characteristics of UHR

Young adults at increased risk of developing psychotic disorders can be identified using standardized psychometric instruments such as the CAARMS with consistent reliability and good predictive value (P Fusar-Poli et al., 2016b). However, there is a particularly wide range of symptoms and presentations in people at Ultra High Risk (UHR) for psychosis, and the population is also markedly heterogeneous in terms of clinical outcome, with some individuals making a complete recovery, others having persistent symptoms, and another subgroup developing a psychotic disorder (P. Fusar-Poli et al., 2016).

Recently preclinical models have been used to help understand the neurobiological mechanisms underlying the onset of psychosis. The methylazoxymethanol acetate (MAM) Model posits a key role for the hippocampal-midbrain-striatal circuit, and suggests that prior to onset of psychosis, hippocampal activity is elevated (Lodge & Grace, 2011). In keeping with this, recent neuroimaging studies in UHR subjects have shown both reduced hippocampal volume and increased hippocampal perfusion relative to controls (Allen et al., 2016; Mechelli et al., 2011; Schobel et al., 2009).

The MAM model suggests that psychotic symptoms are generated when hippocampal hyperactivity drives hyperactivity in subcortical regions involved in dopamine signalling. Changes in hippocampal anatomy and function have been a consistent biological finding in schizophrenia (Heckers, 2001; Preston et al., 2005; Tamminga et al., 2010).

Allen et al. (2015) found evidence of resting state hyperperfusion in the hippocampus, midbrain, and basal ganglia of UHR subjects at clinical presentation; moreover, this hyperperfusion subsequently reduced as the presenting symptoms resolved. In particular, there was a longitudinal reduction in rCBF in the hippocampus and ventral striatum in the subgroup of UHR subjects who showed symptomatic improvement. Similarly, subjects whose symptoms had resolved to the extent that they no longer met UHR criteria showed a reduction in left hippocampal rCBF, whereas those who still met UHR criteria after 18 months or who had become psychotic did not.

These findings are in line with data from a study that measured perfusion with steady-state gadolinium-enhanced fMRI (Schobel et al. (2009). Taken together, these findings support the notion that increased resting hippocampal perfusion is a feature of the UHR state, and is related to the severity of attenuated psychotic symptoms.

3.1.6 Neurobiology of symptoms in UHR

Relatively few neuroimaging studies have investigated the neural correlates of symptoms in UHR subjects.

Using MRI, Smieskova et al. (2012) investigated the relationship between grey matter volume and clinical presentation in the UHR state. They reported that alterations in the volume of the insula were associated with negative symptoms and hallucinations. However, this study looked only at symptoms grouped in to positive and negative categories.

Two studies have looked at total CAARMS score: In a study using F-DOPA PET, Howes et al. (2009) reported that the severity of symptoms in UHR subjects, as indexed by the total CAARMS score, was correlated with the level of striatal dopamine function. However there were no correlations with specific types of symptom, and the finding was not replicated in a subsequent study (Egerton et al., 2013).

To my knowledge, there has yet to be an investigation of the neural correlates of symptom *dimensions* in UHR subjects.

3.1.7 Review of Findings for Each Dimension

The work described in this chapter aimed to investigate the neurobiological correlates of the five psychopathological dimensions in UHR state stablished in the previous chapter. I thus planned to examine the relationship between scores on the Negative, Disorganised – Behavioural, Disorganised -Cognitive, Affective Instability and Anxiety dimensions and resting CBF, measured using ASL.

Negative symptoms in schizophrenia have been shown using PET and SPECT to be associated with decreased resting perfusion in frontal (Erkwoh et al., 1999; Lewis et al., 1992; Sabri et al., 1997), temporal (Esel et al., 2000; Sabri et al., 1997) and thalamic regions (Min et al., 1999; Sabri et al., 1997). Using PET, P. F. Liddle et al. (1992) found associations between a negative symptom dimension with resting blood flow in the right and left caudate, left dorsolateral prefrontal cortex and left superior parietal cortex. More recently, using ASL, a negative symptom dimension in schizophrenia was associated with reduced CBF in the superior temporal and cingulate gyri bilaterally, and in the left middle frontal gyrus (Pinkham et al.

(2011). A number of MRI studies have also linked negative symptoms to reductions in grey matter volume in prefrontal cortex (Chua & Murray, 1996).

Liddle et al (1992) also found that loadings on a Disorganised symptom dimension were associated with increased rCBF in the right anterior cingulate cortex, and decreases in the right ventral prefrontal cortex and insula, and in the parietal cortex. While two studies specifically examining cognitive disorganisation have also found patterns of both increased and decreased perfusion: McGuire et al. (1998) found that verbal disorganisation (positive thought disorder) was inversely correlated with activity in the inferior frontal, cingulate and left superior temporal cortex, and positively correlated with activity in the parahippocampal/anterior fusiform region bilaterally, and in the body of the right caudate, Kircher et al. (2001) found that patients showed less activation in the right superior temporal gyrus than controls, but greater activation in the left inferior frontal, inferior temporal and fusiform gyri.

When compared to healthy volunteers, UHR subjects were reported by Allen et al. (2016) to show elevated rCBF in the hippocampus, basal ganglia, and midbrain. Symptomatic improvement at follow-up was associated with reduced rCBF in the hippocampus and ventral striatum.

The CAARMS measures not only attenuated psychotic symptoms, but also anxiety and mood symptoms. In schizophrenia, comorbid anxiety disorders have been shown to occur in up to 38% of cases (Braga et al., 2013) and presence and severity of symptoms of anxiety were found to be associated with more severe clinical features and poorer outcomes.

The amygdala has been shown to exhibit increased resting CBF in imaging studies of subjects with anxiety disorders (Rauch et al., 2003) and altered activity in the prefrontal cortex is also widely reported in anxiety disorders (Sylvester et al., 2012). Activity in these regions is also known to be robustly altered in people with schizophrenia (Minzenberg et al., 2009; Tseng et al., 2016), who also demonstrate wide-ranging impairments in emotional functioning (Livingstone et al., 2009). A meta-analysis by A. Etkin and Wager (2007) found that patients with a range of anxiety disorders consistently showed greater activity than matched comparison subjects in the amygdala and insula. Thus we predicted that the anxiety factor will be associated with altered rCBF in both amygdala and Insula.

The relationship between Affective Instability symptoms and rCBF has been investigated using SPECT in bipolar disorder finding that patients with mania had significantly reduced perfusion mainly in the left frontal area, also in the left anterior cingulate and parietal cortices (Bhardwaj et al., 2010). The anterior cingulate cortex is a key neural region implicated in mood regulation and processing of negative self-referential information (Price & Drevets, 2010), so this may be reflected in a correlation with Affective Instability symptoms.

3.1.8 Aims and Objectives of this Study

Previous neuroimaging findings in schizophrenia (described above), suggest that the negative and disorganised symptom dimensions may be associated with specific regional patterns of resting rCBF in UHR. A previous ASL study in UHR subjects suggests that total CAARMS severity is associated with increased perfusion in the hippocampus, basal ganglia and midbrain. On the other hand, the

deficits evident in both schizophrenia and anxiety disorders, suggest that altered perfusion in the insula and amygdala may correlate with anxiety symptoms in UHR states. Few studies have examined the neural correlates of Affective Instability symptoms or mania, but Affective Instability symptoms have been shown to be associated with perfusion in the anterior cingulate cortex in patients with bipolar disorder.

Therefore a priori hypotheses about the neural correlates of the five UHR dimensions and the total CAARMS score are proposed here. The analyses used a Regions of Interest (ROI) approach. ROIs were selected on the basis of previous findings, however as these symptoms have not previously been investigated in relation to CBF in UHR, I tested the following non directional hypotheses using this approach:

1. The Negative factor will be associated with the level of perfusion in the dorsolateral prefrontal cortex, dorsal anterior cingulate gyrus and striatum (P. F. Liddle et al. (1992)
2. The Disorganised-behavioural and Disorganised-cognitive factors will be associated with the level of perfusion in the anterior cingulate, ventral prefrontal and parietal cortex (Pinkham et al. (2011).
3. The anxiety factor will be associated with the level of perfusion in the amygdala and insula (A. Etkin & Wager, 2007)
4. The Affective Instability dimension will be associated with the level of perfusion in the basal ganglia, medial frontal gyrus and inferior frontal gyrus (Bhardwaj et al., 2010)

5. The Total CAARMS score will be associated with the level of perfusion in hippocampus, striatum and midbrain (Allen et al. (2016)

Whole brain analyses will also be conducted to determine if there are associations with rCBF in areas other than those represented in the ROIs.

3.2 Method

3.2.1 Sample

The sample comprised a subset of the UHR sample studied in Chapter 2. There were 70 individuals meeting the PACE criteria for Ultra High Risk for Psychosis (UHR), aged 18-35 recruited through a Wellcome Trust funded programme at King's College London (collected by the author). All subjects were recruited through clinical early detection services at three sites:

- OASIS (Outreach and Support in South London), part of the South London and Maudsley NHS Trust, (n=47)
- West London Early Intervention Service, part of the West London Mental Health NHS trust (n=7)
- CAMEO, part of the Cambridge and Peterborough NHS trust (n=23)

The study had National Research Ethics Service (NRES) approval and all participants gave written informed consent to participate.

3.2.2 Eligibility Criteria

Participants were recruited from specialist early intervention services and assessed by trained researchers. According to the PACE criteria, an individual can be classed as UHR if they meet the threshold for one or more of the following subcategories:

Group 1: Attenuated Psychotic Symptoms (APS) sub-threshold in frequency or intensity

Group 2: Brief Limited Intermittent Psychotic Symptoms (BLIPS) that resolved within a week without use of anti-psychotic medication

Group 3: Genetic risk combined with a significant recent decline in functioning.

(The decline in functioning was only an inclusion criterion in the Genetic Risk group)

Inclusion required that participants:

- Met UHR criteria
- Were aged 18 - 35

The exclusion criteria were:

- Neurological or medical illness or head injury
- Meeting DSM-IV criteria for drug/alcohol abuse or dependency
- Pregnancy
- Treatment with antipsychotic medication for a week or more
- Claustrophobia (preventing the subject from completing the scan)
- Metallic tattoos
- Cardiac pacemaker
- Implanted catheter, clamp, clips, valves, or other metal
- Insulin or infusion pump

3.2.3 Measures

UHR status was determined using the Comprehensive Assessment of At Risk Mental State (CAARMS). This is described in detail in section 2.2.3.

Severity and Frequency are scored on a scale of 0-6, and distress is scored as a subject reported percentage. As in previous studies, the Severity score was used to calculate total and dimension scores.

Intake group was defined using CAARMS criteria. Sub-threshold intensity Attenuated Psychotic Symptoms are classified as a severity score of 3-5 and frequency score of 3-6 on any of the items in the Positive scale; Sub-threshold frequency Attenuated Psychotic Symptoms are classified as a frequency score of 3 and a severity score of 6 on any of the items in the Positive scale. Brief Limited Intermittent Psychotic Symptoms (BLIPS) are defined as a severity score of 6, with frequency greater than 4 on any of the items in the Positive scale, but each symptom is present for less than one week, with spontaneous remission.

The CAARMS was implemented by a trained researcher. Inter-rater reliability was ensured via online training tools for the CAARMS incorporating inter-rater reliability standard requirement for completion of the training. Language inconsistencies for centres not conducting assessments in English was address through back translation.

Symptom Dimensions were determined using factor analysis described in the previous chapter. Unit weighted composite scores for each dimension were calculated as a mean score of all the items loading on the respective factor. A

diagram of the dimensions and the symptoms that they include is shown in figure 4 in section 2.3.4.

3.2.4 pCASL Protocol

Arterial spin labelling (ASL) is a relatively new and non-invasive perfusion imaging modality that can be used for visualization and quantification of CBF. Arterial spin labelling uses magnetically labelled arterial blood water protons as an endogenous tracer of flow. In Continuous ASL (CASL), the 'labelled' image is acquired after the inversion of the arterial water spins by an adiabatic sequence consisting of a relatively long off-resonance radiofrequency pulse and a constant gradient in the direction of the flow (Williams et al, 1992). A 'control' image is also acquired after the same sequence but with a sine-modulated radiofrequency pulse to ideally produce no net magnetic inversion of the spins (Alsop and Detre, 1998). A CBF image is computed by subtracting the labelled from the control image and then applying a set of measured or assumed physiological and MRI parameters to obtain voxel-wise flow values in absolute units (i.e., mL/100 g/min).

For this study subjects were scanned with their eyes open using a General Electric Signa HDX 3.0T scanner, fitted with a receive only 8-channel phased array head coil at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London. For image registration both a high resolution T2-weighted Fast Spin Echo (FSE) image (0.468x0.468x4mm, TE=54.58ms, TR=4380ms, Flip angle 90deg, FoV=240) and a high-resolution T1-weighted Spoiled Gradient Recalled (SPGR) image (1.1x1.1x1.1mm, TE=2.848, TR=7.144ms, Flip angle=20deg, FoV=280) were acquired. Resting Cerebral Blood

Flow (rCBF) was measured using Continuous Arterial Spin Labelling (CASL) scans acquired with a 3D Fast Spin Echo (FSE) spiral multi-shot readout, following a post-labelling delay of 1.5s.

The spiral acquisition used a short (4ms) TE, and 8 spiral arms (interleaves) with 512 points in each arm. (FSE TE 32ms/TR = 5500ms; ETL = 64). Images were reconstructed to a 2562 matrix, giving a final spatial resolution of 1x1 mm in plane. 60 slices of 3mm thickness were obtained. Three pairs of tagged-untagged images were collected. Background suppression included selective saturation of the image slab at 4.3s before acquisition, selective inversion 3s before acquisition and non-selective inversions at 1.5s, 764ms, 334ms and 84ms before imaging. This repeated inversion achieved successful suppression of the background static tissue signal, maximizing the sensitivity to blood perfusion.

Calibration images were collected with the same imaging sequence but with inversion recovery preparation instead of CASL. One sequence with saturation of 4.3s and then an inversion at 1650ms before imaging was used to create a fluid suppressed image. A second sequence with saturation at 4.3s and then inversion at both 2408ms and 511ms was also acquired to create a fluid and white matter suppressed image. For both these sequences, the receiver gain was automatically lowered by 21 dB relative to the ASL sequence to avoid receiver saturation. These images were used to quantify blood flow in physiological units (ml blood/100gm tissue/min).

The sensitivity of the image to water was calibrated at each voxel 1-3. When multi-channel coils are employed, the spatially non-uniform sensitivity complicates this

calibration. Often the underlying tissue signal is used as an indicator of water sensitivity, but a water density in each voxel, or partition coefficient, must then be assumed. We observed that the signal intensity in the inversion-prepared fluid-suppressed image was relatively constant for different tissues. This is likely because more complete recovery occurs for shorter T1 tissues, which tend to have lower water density.

Using a neighbourhood maximum algorithm to avoid regions with partial volume of suppressed fluid, a low resolution sensitivity map was created. This map was calibrated for water sensitivity by assuming the tissue was white matter with a water concentration of 0.735 gm/ml 4 and a T1 of 900ms, and using the equations for inversion recovery signal attenuation. By assuming grey matter with a water concentration of 0.88 gm/ml and a T1 of 1150 there was only a 5% calibration difference. This calibration produced a sensitivity map, C, equal to the fully relaxed MRI signal intensity produced by 1gm of water per ml of brain tissue.

With this co-registered sensitivity map C, we calculated cerebral blood flow (CBF) using the equation:

$$CBF = \frac{\rho_b\left(S_c - S_l\right)}{2\alpha C\,\omega_a T1_a \exp\left(-\frac{w}{T1_a}\right)\left(1-\exp\left(-\frac{tl}{T1_a}\right)\right)}$$

Where ρb is 1.05g/ml (the density of brain tissue;4, α is the labelling efficiency (assumed to be 95% for labelling times 75% for background suppression; 5, w is 1.5s (the post-labelling delay;2, tl is 500ms (the labelling duration), T1a is 1.4 ms

(the T1 of arterial blood which was slightly lower than the value of Lu et al. 2004), ωa 0.85 g/ml (the density of water in blood; 4, Sl and Sc are the signal intensities in the labelled and control images, respectively).

The whole ASL pulse sequence, including the acquisition of calibration images, was performed in 6:08min. Images were acquired on the same day as the CAARMS was administered.

3.2.5 Image Pre-processing

Arterial spin labelling allows the quantification of resting cerebral blood flow (rCBF) measures in units of ml/100g of tissue/second. To maximise the correspondence between regional perfusion and neural activity, p-CASL images were acquired after a long (1.5s) post-labelling delay, to ensure that the data reflected perfusion at the level of capillary micro-circulation, which is most closely associated with neural function (Hirano et al., 2011).

For each participant, one Spoiled Gradient Recalled (SPGR) scan was used in the pre-processing steps in addition to the T2 images acquired at the time of the CASL image, which ensured that the normalization parameters applied to each scan were identical for each individual.

The following steps were then taken:

I. Extra-cerebral signal from the T2 scan was removed using the “Brain Extraction Tool” (BET) of FSL 7. The skull stripped T2 volume and its corresponding binary mask were then co-registered to the rCBF map.

II. The co-registered binary mask was multiplied by the rCBF map to remove extra-cerebral signal from this scan. The skull stripped T2 and rCBF maps were then co-registered back to the space of the original T2 scan (returned to their original frame of reference).

III. The T2 scan was subsequently co-registered to each subjects structural (SPGR) scan, with the co-registration parameters applied to the corresponding rCBF maps and brain extracted T2 scans

IV. The SPGR was normalized to MNI space using a non-linear approach using FNIRT 8 (FMRIB Non-linear Image Registration Tool) and the transformation matrix was applied to the rCBF map and the T2 scans.

V. All data were then smoothed using a 6 mm Gaussian Smoothing kernel.

3.2.6 Image Analysis

Statistical analyses of rCBF data were performed using Statistical Parametric Mapping (SPM) Version 8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8).

The dimensional structure described above was then used to determine a mean score for each participant for each dimension. Unit weighted composite dimension scores were applied as contrasts in SPM.

For the Negative, Disorganised and total CAARMS score, regions of interest based on the hypotheses in section 3.1.8 were defined using the MNI coordinates determined from the corresponding previous study. A small volume correction (SVC) with a 6mm sphere was applied in the statistical analysis.

For the Negative factor the coordinates were taken from Pinkham et al. (2011):

- Right superior temporal gyrus (55, -55, 10)
- Left inferior frontal gyrus (-59, 18, 8)
- Anterior Cingulate gyrus (0, 3, 27)
- Left middle frontal gyrus (− 32, 15, 36)

The Pinkham study did not examine a disorganised dimension, only positive and negative symptoms. The coordinates for the Disorganised-behavioural and Disorganised-cognitive factors were therefore taken from Liddle et al. (1992):

- Right anterior cingulate (8, 30, 16)
- Mediodorsal thalamus (2, -2, 4)
- Right ventrolateral prefrontal cortex (26, 32, 0)
- Right angular gyrus (42, -60, 8)
- Left angular gyrus (-40, -74, 16)

For the total CAARMS scores, the coordinates were taken from Allen et al. (2016):

- Left subiculum/hippocampus (-22 -28 -8)
- Right subiculum/hippocampus (20 -28 -8)
- Right pallidum (22 -12 -4)
- Left pallidum/putamen (-18 -8 -4)
- Left midbrain (-10 -32 -18)

For the Anxiety and Affective Instability dimensions, as there were no studies directly examining these symptoms in UHR, pre-defined anatomical masks were used, as provided by the AAL software using the WFU_Pickatlas toolbox in SPM8.

For the Anxiety Dimension a mask of the amygdala and insula was used (A. Etkin & Wager, 2007), for the Affective Instability dimension a mask of the basal ganglia, medial temporal gyrus, and inferior frontal gyrus was used (Bhardwaj et al., 2010).

ROI analyses are reported at a corrected voxel-wise level of P <.05 Family Wise Error (FWE). Exploratory whole brain analyses were conducted at $p < .001$ $K_E > 50$ and results were considered significant if they survived cluster level family-wise error (FWE) correction ($p < .05$). Findings that were evident at an uncorrected threshold of $p<0.001$ are reported as trends.

As antipsychotic medication is known to affect rCBF (Handley et al., 2013), additional confirmatory analyses were conducted after subjects who were receiving antipsychotic medication had been excluded.

3.3 Results

3.3.1 Sample Characteristics

The average age of the sample was 22 years and 4 months of age (range: 18-36), with 59% males and 67% of white ethnicity, with the remainder belonging to minority ethnic groups. Eight of the participants were being treated with low doses of antipsychotic medication (Quetiapine n=4; Olanzapine n=2; Risperidone n=2). Demographic information is shown in table 12 below.

Table 12: Demographic Characteristics of sub-sample used for ASL Analysis

		Wellcome Study
Sample Size		70
Age	**Mean**	22.37
	SD	3.93
Gender (male)		41 (59%)
Ethnicity	**White**	47 (67%)
	BME	23 (33%)
Intake Group	**APS**	70 (100%)
	BLIP	5 (7%)
	Genetic Vulnerability	2 (3%)

3.3.2 Clinical Characteristics

Seventy five subjects met UHR criteria for Attenuated Psychotic Symptoms (APS), five had experienced Brief Limited Intermittent Psychosis, and two had a combined genetic vulnerability (first degree relative with diagnosis of schizophrenia or previous diagnosis of schizotypal personality disorder).

CAARMS total scores ranged from 13 to 81, with an average score of 42. Dimension scores were calculated as a mean of items that loaded on each factor as determined in the factor analysis in the previous chapter. Information on CAARMS total scores and dimension scores are shown in table 13 below.

Table 13: Mean, Standard Deviation and range of CAARMS Scores of 70 UHR subjects

		Min	Max	Mean	SD
CAARMS Total Score		13	81	42.47	17.11
Mean Dimension Scores (0-6)	**Negative**	0	4.75	2.31	1.24
	Disorganised - Behavioural	0	3.25	0.49	0.63
	Disorganised – Cognitive	0	3.25	1.48	0.80
	Affective Instability	0	4.33	1.89	1.27
	Anxiety	0	4.25	2.28	1.09

3.3.3 Total CAARMS score and rCBF

ROI Analysis:

ROI analysis in the regions specified from Allen et al. (2016) revealed a significant correlation between the total CAARMS score and decreased rCBF in the left hippocampus. Results are shown in the table 14 below. No significant correlation was found in the right hippocampus, left pallidum, left midbrain or right pallidum. SPM output is shown in Appendices 7-9.

Table 14: Table showing significant results of ROI analyses for correlation with total CAARMS Score

Region	Cluster Size	Z Statistic	P (FWE) corrected	x	y	z
Left hippocampus	14	3.54	0.002	-28	-28	-8

Whole brain analysis:

Whole brain analysis showed that there were trends ($p<.001$, uncorrected) for the total CAARMS score to be negatively correlated with perfusion in the parahippocampal gyrus (x, y, z = -30, -26, -12; Z = 3.88; KE = 210), cerebellum (x, y, z = -8, -78, -16; Z = 4.15; KE = 278), right thalamus (x, y, z = 16, -18, 12; Z = 3.92; KE = 222), and superior frontal gyrus (x, y, z = -28, 54, -4; Z = 3.54; KE = 54). However, after FWE correction, only the negative correlation in the left thalamus remained significant (x, y, z = -10, -40, -2; Z = 3.86; $K_E = 719$; $p_{FWE} = 0.041$).

Results are shown in figure 10 and SPM output is given in Appendix 4.

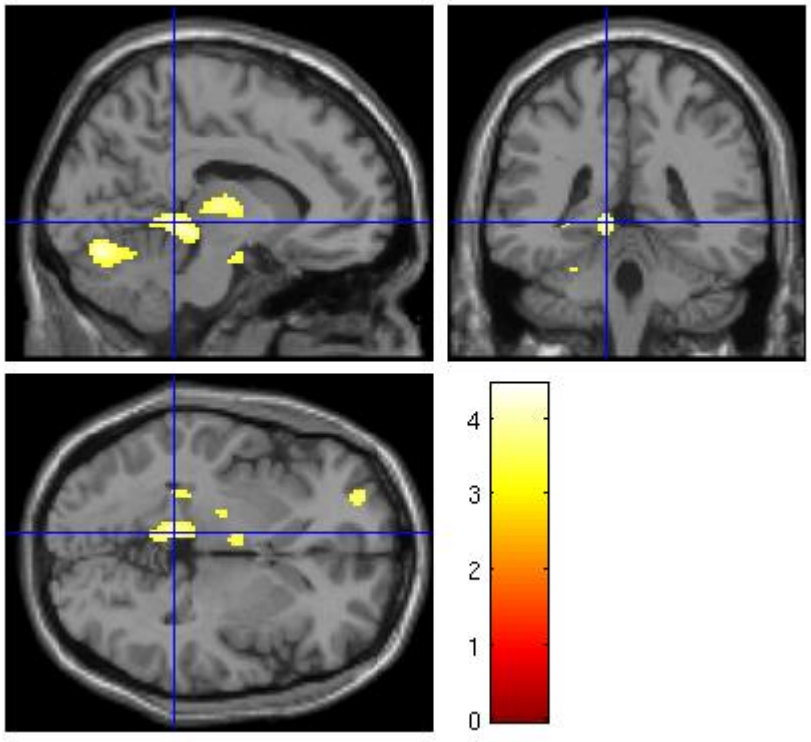

Figure 10: Statistical parametric maps showing rCBF correlation with Total CAARMS score (p = .05 FWE Corrected).

3.3.4 Negative Dimension and rCBF

ROI Analysis:

ROI analysis of the 5 regions specified in (Pinkham et al., 2011) found no significant correlations between Negative dimension scores and rCBF in any area.

Whole brain analysis:

Whole brain analysis found no significant correlations between Negative dimension scores and rCBF.

3.3.5 Disorganised dimensions and rCBF

ROI Analysis:

ROI Analysis in the areas specified by Liddle et al. (1992) showed a significant correlation between decreased perfusion in the mediodorsal thalamus and scores on the Disorganised – Behavioural dimension. Results are shown in table 15 below. There were no significant correlations between Disorganised – Behavioural or Disorganised - Cognitive dimension scores and the right anterior cingulate, right ventrolateral prefrontal cortex, or angular gyri ROIs. SPM output is shown in Appendix 10

Table 15: Table showing significant results of ROI analyses for correlation with Disorganised – Behavioural scores

Region	Cluster Size	Z Statistic	P (FWE) corrected	x	y	z
Mediodorsal thalamus	93	4.09	0.000	-4	-20	4
		3.44	0.000	8	-20	4

Whole brain analysis:

Scores on the Disorganised – Behavioural dimension were negatively correlated with perfusion in the left hippocampus (x, y, z = -30, -28, -8; Z = 4.51; K_E = 2944; p_{FWE} = 0.002), the left cerebellum (x, y, z = -20, -88, -18; Z = 4.09; KE = 1378; p_{FWE} = 0.003), and the occipital gyrus (x, y, z = -32, -84, 30; Z = 4.04; KE = 1964; p_{FWE} = 0.001).

There were additional trends (p<.001, uncorrected) for negative correlations with rCBF in the inferior and middle temporal (x, y, z = -38, -84, 12; Z = 3.77; KE = 213;

x, y, z = 58, -60, 4; Z = 3.69; KE = 37), inferior frontal (x, y, z = -18, 30, -2; Z = 3.48; KE = 69), and postcentral gyri (x, y, z = -56, -24, 22; Z = 3.23; KE = 116).

The results are shown in figure 11 and SPM output is given in Appendix 5.

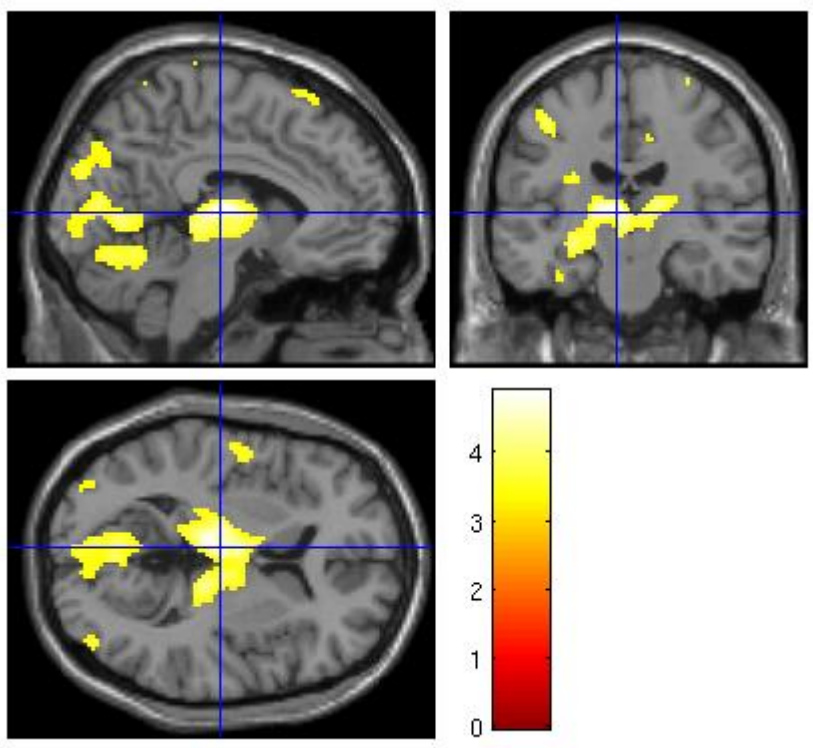

Figure 11: Statistical parametric maps showing rCBF correlation with Disorganised dimension scores (p = .05 FWE Corrected).

3.3.6 Anxiety dimension and rCBF

ROI Analysis:

ROI analysis in the insula and amygdala in a single mask showed a significant negative correlation between rCBF in the left insula and anxiety scores (x, y, z = -44, 8, 4; Z = 3.56; KE = 63, p_{FWE} = 0.03). Results are shown in figure 12 and SPM output is shown in Appendix 11.

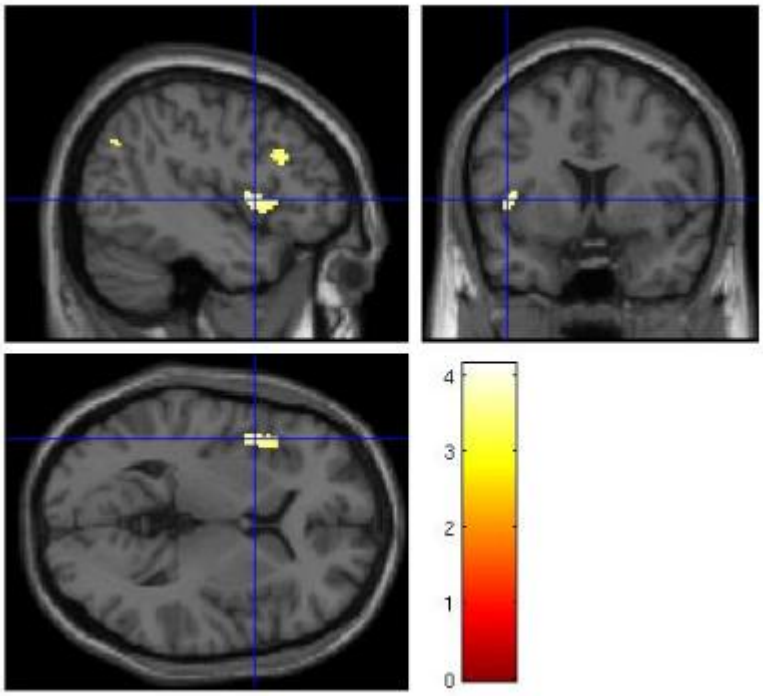

Figure 12: Statistical parametric maps showing rCBF correlation with Anxiety dimension scores (p = .05 FWE Corrected).

Whole brain analysis:

There were no correlations with scores on the Anxiety dimension that survived FWE correction. There were trends (p<.001, uncorrected) for negative correlations with rCBF in the right medial frontal (x, y, z = 12, 28, 38; Z = 3.51; KE = 72), left inferior frontal (x, y, z =-32, 32, -14; Z = 3.65; KE = 33), and left angular gyri (x, y, z =-44,-66, 36; Z = 3.21; KE = 6), and in the left insula (x, y, z =-44, 8, 4; Z = 3.90; KE = 183).

Results are shown in figure 13 and SPM output is given in Appendix 6.

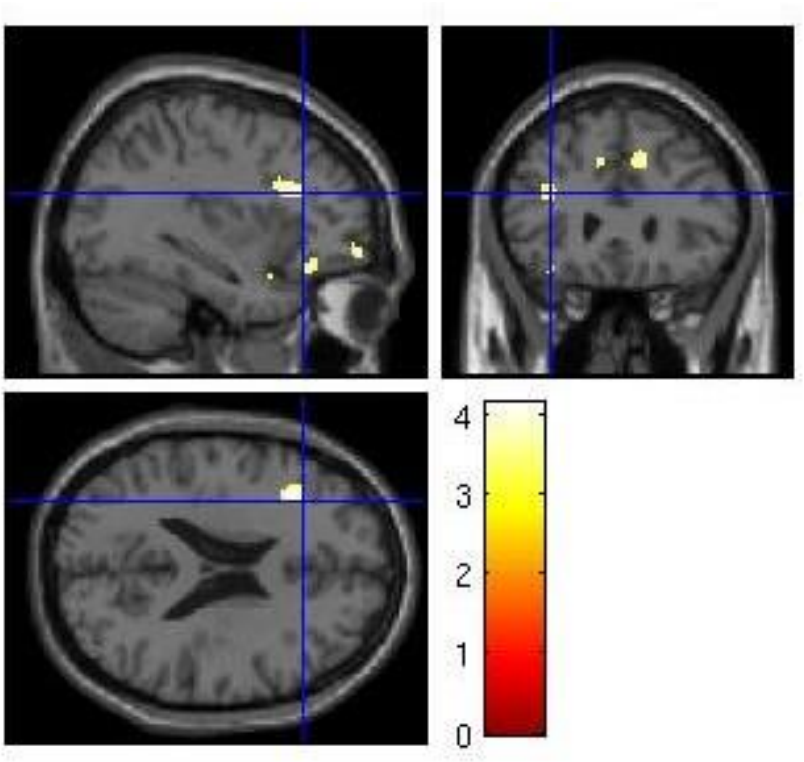

Figure 13: Statistical parametric maps showing rCBF correlation with Anxiety dimension scores (p = .05 FWE Corrected).

3.3.7 Affective Instability dimension and rCBF

ROI Analysis:

ROI analysis of the 5 regions specified in Bhardwaj et al. (2010) found no significant correlations between Affective Instability dimension scores and rCBF in any area.

Whole brain analysis:

Whole brain analysis found no significant correlations between Affective Instability dimension scores and rCBF.

3.3.8 Summary of Significant Results (after correction for multiple comparisons)

The ROI analysis indicated that Disorganised – Behavioural dimension was associated with decreased perfusion in the mediodorsal thalamus, while whole brain analysis revealed additional associations with decreased perfusion in the left hippocampus, cerebellum and occipital gyrus.

The ROI analysis indicated that the total CAARMS Score was associated with decreased perfusion in the left hippocampus, the left pallidum, and the left midbrain, while whole brain analysis revealed an additional association with decreased perfusion in the left thalamus.

The ROI analysis for the Anxiety Dimension showed a negative significant correlation with perfusion in the insula.

3.4 Discussion

3.4.1 Aims and Results of the Study

This study examined the relationship between resting cerebral blood flow and severity scores on CAARMS symptom dimensions and the CAARMS total score in a sample of 70 UHR subjects. The results showed a significant correlation between total CAARMS severity and rCBF in the left thalamus, as well as finding significant decreases in CBF in three ROI's specified by Allen et al. (2016): the left hippocampus, left pallidum and left midbrain. ROI analysis of Negative dimension scores did not show any correlation between negative dimension scores in the areas specified by Pinkham et al. (2011), however there were significant

reductions in CBF in one of the areas identified by P. F. Liddle et al. (1992): mediodorsal thalamus and the Disorganised – Behavioural dimension. Whole brain analysis based on the different psychopathological dimensions revealed significant negative correlations between scores on two of the five dimensions: Disorganised – Behavioural with left hippocampus, left cerebellum and occipital gyrus; and Anxiety with medial and inferior frontal gyrus, although this finding did not survive correction for multiple comparisons.

3.4.2 Comparison with Previous Studies

The findings for the Disorganised - Behavioural dimension produced three robust, significant findings in three large clusters in the left hippocampus, left cerebellum and occipital gyrus, as well as replicating a previous finding from (Liddle et al., 1992) in an ROI analysis of the mediodorsal thalamus.

The hippocampus has been consistently shown to play a key role in cognitive organisation in both animal models (Wesierska et al., 2005) and humans (Olypher et al., 2006). In schizophrenia, several studies have found a link between disorganisation and hippocampal rCBF / volume (Chua et al., 1997; McGuire et al., 1998; Prasad et al., 2004), and it has also been one of the most robust neurobiological findings in UHR (Allen et al., 2015; Allen et al., 2016; Schobel et al., 2009). However, this study only examined scores within UHR subjects, and found that perfusion decreased with higher scores in the disorganised dimension, whereas previous studies have shown that when UHR subjects are compared with healthy controls, increased hippocampal perfusion is evident in the UHR group (Allen et al., 2016). This contrast may be due to the within group design of the

study – examining only severity of symptoms and rCBF between patients, rather than comparing patients with controls, or may be due to the differential patterns of individual symptoms (in this case Disorganised) rather than looking at the UHR group as a whole.

The significant correlation of disorganised symptoms with perfusion in the thalamus is in a replication of the P. F. Liddle et al. (1992) finding in schizophrenia and in keeping with Pollak et al. (2015), who found a significant association with perfusion in the pulvinar and ketamine-induced disorganised symptoms. The pulvinar nucleus projects to several cortical areas, including prefrontal and limbic regions, as well as having projections to and from sensory cortices. Disruption to this region can produce deficits in verbal and non-verbal processing (Ojemann et al. 1968) and its function is abnormal in schizophrenia (Andrews et al. 2006).

The cerebellum is historically considered part of the motor system that integrates information from sensory systems of the spinal cord and from other parts of the brain to fine tune motor activity (Fine et al., 2002). The finding of a negative correlation between the Disorganised - Behavioural dimension and CBF in the cerebellum makes sense with the inclusion of motor symptoms such as Impaired Motor Function in the dimension. The cerebellum has been linked to development of psychosis (Marcelis et al., 2003) and a recent meta-analysis found decreased activity in the cerebellum in schizophrenia (Matheson et al., 2014) as well as consistent findings in UHR (J. A. Bernard et al., 2014; Pantelis et al., 2003; Ziermans et al., 2012).

The correlation of disorganised symptoms with perfusion in the anterior cingulate, right ventrolateral prefrontal cortex, or angular gyri that were found in by Liddle et al. (1992) were not replicated in the regional analysis in this study.

The whole brain findings examining all CAARMS symptoms found decreased perfusion in a smaller cluster in the thalamus. There is considerable evidence that the thalamus and associated cortical connections are abnormal in psychotic disorders (Cronenwett & Csernansky, 2010; Sim et al., 2006) and reduced resting state connectivity (Woodward et al., 2012) and volume (Qiu et al., 2009) have been found in psychosis. More recently the thalamus has been found to play a key role in the developmental course of schizophrenia (Walker et al., 2008) and the development of positive symptoms in UHR (Jessica A. Bernard et al., 2015). This ties in with the inclusion of positive symptoms in the overall CAARMS scores, but not in the dimensional scores.

Abnormalities in the thalamus have been found in UHR using other imaging modalities. Glutamate in the thalamus has been found to be reduced in UHR subjects (Egerton et al., 2013; Stone et al., 2009) and thalamic volume is reduced in UHR (Dietsche et al., 2017) and schizophrenia (Adriano et al., 2010; Buchmann et al., 2014).

The regional analysis of the total CAARMS score found decreased perfusion in the left hippocampus, left basal ganglia and left midbrain was evident as with higher total CAARMS scores. This is in direct contrast to the findings by Allen et al. (2016) where elevated rCBF in the hippocampus, basal ganglia, and midbrain was found in UHR compared to controls, and symptomatic improvement was associated with

a reduction in rCBF in the hippocampus and ventral striatum. The present study involves a within-UHR analysis as opposed to UHR vs controls. The brain changes associated with UHR state may not purely reflect the presence of symptoms measured by the CAARMS – there is also a functional impairment, cognitive impairments and probably genetic vulnerability to psychosis. There is some evidence that the GAF score is associated with rCBF in First Episode Psychosis (FEP) (Koike et al., 2016), however this has not yet been shown for cognition and genetic load.

Although none of the whole brain findings for the Anxiety dimension survived correction for multiple comparisons, the findings in the medial and inferior frontal gyrus were in keeping with previous studies: both the medial and inferior frontal gyrus have been shown to play a role in threat-induced anxiety (Gold et al., 2015), trait anxiety (Modi et al., 2015) and impaired cognitive function associated with anxiety (Minzenberg et al., 2009). Finally, reduced insula volume has been shown in schizophrenia patients (T. Takahashi et al., 2005) and it has been shown to be hyperactive in anxiety disorders (A. Etkin & T. D. Wager, 2007). The insula and amygdala are directly anatomically connected in a reciprocal manner and studies have proposed insula–amygdala interactions on the basis of the finding that both structures are activated conjointly and similarly during experimentally induced anxiety (Carlson et al., 2011; Phelps et al., 2001). Thus, although this finding also did not remain significant, it aligns with previous findings.

The ROI analysis based on the Anxiety dimension, showed a significant association between higher Anxiety scores and lower CBF in the insula. This is in direct

contrast to what would be expected and what has been found previously (A. Etkin & Wager, 2007). A possible explanation for this may be reached when examining the items that are included in this dimension. Anxiety and Impaired Tolerance to Normal Stress are typical anxiety symptoms and may be expected to correlate with increased perfusion, however Impaired Role Function and Social Isolation, which group with the Anxiety symptoms in this model are more likely to be considered negative symptoms. It may be that the cooccurrence of these symptoms in one dimension are distorting the findings that would be expected for symptoms of anxiety.

3.4.3 Limitations

Although many of the findings in this study are consistent with previous studies in both UHR and schizophrenia, they should be considered in the context of potential limitations.

Although most UHR subjects were medication-naïve, a small number (8 of 70) had been treated with low doses of antipsychotic medication. Medication in these subjects may have altered the severity of their psychotic symptoms, and may also have direct effects on activity and rCBF (Goozée et al., 2014). However, as only 11% of the sample had been treated, this is unlikely to have had a major impact on the results.

The symptom ratings were not conducted at exactly the same time as the ASL scans, so it is possible that the symptom levels at the time of scanning were different to those at clinical presentation. The pattern of activity associated with psychotic symptoms can vary within subjects over time. For example, several

studies have shown that resting cortical activity varies within patients with schizophrenia over time in the presence or absence of auditory and visual hallucinations (McGuire et al., 1993; Shergill et al., 2001).

Liddle (1992) previously sought to address this issue by defining symptom dimensions on the basis of symptom scores that were stable over a prolonged period of time in patients with chronic schizophrenia. However, although 2-year follow up CAARMS data was collected, this was not feasible in the present study as UHR subjects symptoms are more likely to change quickly over time than in chronic patients. Ideally, subjects would be rated on the CAARMS e.g., every day for 5 days and then the average scores could be used to define the dimensions. However, this would be logistically demanding and difficult to implement in practice.

The validity of the symptom dimensions also depends on the accuracy and reliability of the CAARMS ratings. Although both trained raters completed training and met inter-rater reliability standard requirements before implementing the CAARMS, there were two different raters, and most of the symptoms ratings are subjective, which relies on full disclosure from the subject. If the UHR subject is guarded about revealing symptoms the scores may not reflect the true psychopathology.

CAARMS scores may also be influenced by substance use. 13 subjects reported that positive symptoms occurred in relation to substance use as well as at other times as well. However this rating is only included in the positive symptom scale, and may affect other symptoms.

3.4.4 Future Research Directions

These findings are derived from the first examination of symptom dimensions and CBF in UHR, and will therefore need replication. It would also be interesting to examine CBF and symptom dimensions in a longitudinal context. It has been shown that CBF normalises with improvement in the total CAARMS score (Allen et al., 2016), and further work is needed to determine the stability of symptom dimensions and their neurobiological correlates over time.

As a reflection of neural activity, the regional CBFs of different brain regions are not independent. Instead, the CBFs of brain regions from the same functional network may change synchronously to fulfil the function of the network (Melie-García et al., 2013). This is also true of the symptom dimensions, which are not independent. It may add to the understanding to examine CBF in subjects longitudinally, as symptomatic presentation changes, to determine neural correlates of such change.

This study is an initial exploration of neural correlates of symptom dimensions in UHR, and provides some degree of pathophysiological validation to the previously identified symptom constructs. However, both the statistical and neurobiological exploration of these dimensions has included only baseline information and therefore further examination of these constructs and their correlates over time will be able to expand these findings.

4 Clinical Correlates of Symptom Dimensions

4.1 Introduction

4.1.1 Symptom Dimensions and Outcome in Psychosis

In order to clarify the degree to which psychotic symptoms are predictive of course and outcome of illness, it is necessary to relate dimensions longitudinally to follow up information. This relationship has been examined in psychosis extensively, with many studies concluding that symptom dimensions prove to be a more powerful tool in explaining variance of outcome than categorical sub-diagnoses (Russo et al., 2014; Salokangas, 2003).

An initial exploration of psychopathological syndromes and their association with course and outcome was conducted by van Os et al. (1996), who found negative and disorganised symptom dimensions in patients with psychosis were associated with a worse course of illness.

Although there is not a consistent agreement on the factor structure present in psychosis, with results varying according to the categorical diagnosis of the subjects included and the instrument used to measure symptomatic presentation (Wallwork et al., 2012), the association between negative and disorganised dimensions and poor outcome has been replicated for both negative (Levine & Leucht, 2013; Rabinowitz et al., 2012; Salokangas et al., 2002), and disorganised dimensions (Manuel J Cuesta et al., 1994; Ortiz et al., 2013; Owens et al., 2010) by many studies since. More recent studies such as that by Sánchez-Torres et al. (2017), found that lifetime negative symptoms predicting poor functional outcome

in schizophrenia and disorganization symptoms showed the greatest impact in functioning, preventing patients from achieving remission (Ortiz et al., 2015).

These consistent findings across schizophrenia spectrum disorders, particularly for negative and disorganised dimensions, indicate that a similar pattern of differentiation of outcomes according to symptomatic presentation may be present in UHR.

4.1.2 Outcomes in the UHR Population

In order to examine the relationship between dimensions and outcome in the UHR population, we must ascertain definitive outcome measures, as this group does not have a categorically defined diagnosis or course of illness.

Outcome Defined by Transition to Psychosis:

The UHR criteria use the clinical risk factors, such as functional decline and prodromal symptoms, to determine those who have an imminent risk of developing a psychotic disorder. Thus, the predominant aim in investigating this population is to determine risk factors for the development of psychosis. Initial studies examining the rate of transition to psychosis found high rates of 30 - 40% within one year (Cannon et al., 2008; Yung et al., 2003). A recent meta-analysis found lower rates of transition, with a rate of 22% after 1 year, 29% after 2 years, and 36% after 3 years (Fusar-Poli et al., 2012); however, several studies found transition rates as low as 10% (Demjaha et al., 2010; Lemos-Giráldez et al., 2009; McGorry et al., 2008). In fact, the meta-analysis conducted by Fusar-Poli et al. (2012) found a significant reduction in transitions rates over time. These low transition rates mean that meeting UHR criteria, although indicative of a

significant increase compared to the general population, is not indicative of a psychosis prodrome in the majority of subjects, and it is therefore important to determine outcome not only according to transition.

A meta-analysis in 2011 found that although on average 76% of UHR subjects did not transition to psychosis; over half of the 31 studies included provided no characteristics of those UHR subjects who did not develop psychosis. Since then, several studies have investigated the outcome in those who do not transition to psychosis, and for instance Jean Addington et al. (2011) found that at least one attenuated positive symptom was still present for 43% of the UHR sample after 1 year and for 41% after 2 years. Furthermore, social and role functioning were significantly poorer in the clinical sample relative to controls. Furthermore, Lin et al. (2015) found that individuals at UHR for psychosis who do not transition to psychosis are at significant risk for continued attenuated psychotic symptoms and persistent or recurrent disorders, with 68% experiencing non-psychotic disorder over a two year follow up.

An examination of comorbid disorders in UHR by Fusar-Poli et al. (2014) found that 73% of UHR subjects had a comorbid diagnosis of anxiety of depression and that comorbidity was not associated with transition to psychosis but rather with poor global functioning. There has therefore been a recent focus on risk for non-psychotic disorders and functional outcome.

Both these findings point to the importance of a functionally defined outcome as well as transition to psychosis. Although initially the primary outcome of interest in investigation of the UHR population has been the development of psychotic

disorder, Lin et al. (2012), argued that it is important not to consider only the arbitrary threshold at which psychotic symptoms progress from attenuated to frank psychotic disorder, but that defined outcome in UHR should be broadened to incorporate non-psychotic diagnoses, functioning and negative symptoms.

Outcome Defined by Level of Function:

Lin et al. (2011) proposed that the detection of UHR individuals with poor functioning at follow-up may yield a valid group in which to study biomarkers and treatment of schizophrenia. Deficits in function have long been recognised as a key factor in psychosis, causing a significant and long-lasting health, social, and financial burden, not only for patients but also for families, other caregivers, and the wider society (Knapp et al., 2004). It has also been highlighted as a substantial economic burden on society, with Wu et al. (2005) estimating that functional disability accounts for up to 52% of the costs associated with schizophrenia. Even when positive symptoms are in remission, this does not necessarily coincide with a functional recovery, especially in the early stages of the illness (Robinson et al., 2004), and it is therefore crucial to understand the factors leading to long-term disability in psychotic disorders.

van Os et al. (1999) found that different symptoms dimensions are associated with different levels of functional and social outcome across a large sample of chronic psychotic illnesses, and subsequently, both negative (Levine & Leucht, 2013; Rabinowitz et al., 2012; Salokangas et al., 2002), and disorganised (Manuel J Cuesta et al., 1994; Ortiz et al., 2013; Owens et al., 2010) symptom dimensions have been shown to determine functional outcome in multiple studies.

In UHR, several studies support the increasing emphasis on functional decline as a critically important outcome to be considered alongside the rate of transition to psychosis (Cornblatt et al., 2012; Schlosser et al., 2012). It is important to determine to what extent UHR subjects who do not transition to psychosis represent false positives. Subjects can only be considered to be no longer at imminent risk for psychosis if presenting symptoms and functional deficits that define the UHR status remit within the follow up period. Although Addington et al. (2011) found that subjects that did not transition in the North American Prodrome Longitudinal Study cohort showed symptomatic and functional improvement after 2 years, a significant proportion still met UHR criteria. This is also the case in the PACE sample, with 23% of non-transition cases still meeting APS criteria after 2 years, and 68% meeting diagnostic criteria for at least one non-psychotic disorder (Lin et al., 2015). This suggests that both psychosis and long-term functional disability are equally important targets for prevention (Carrión et al., 2013). Functional disability, as well as an important consideration as an outcome measure on its own merit, has also been show to increase the risk of transition (Dragt et al., 2011; Velthorst et al., 2010).

The identification of factors that reliably differentiate UHR subjects that are at high risk for long term functional impairments from those who are not may provide a framework to understand the disability associated with both those who transition and those who do not. Moreover, this approach may lead to better understanding of the underlying mechanisms of functional impairments at a critical phase in the illness, and inform advancements in improved interventions

for those at an increased risk for functional disability, as well as those at risk of transition to psychosis.

4.1.3 Symptom Dimensions and Outcome in UHR

Symptom Dimensions and Transition to Psychosis:

There have been inconsistent links between individual symptoms and risk of transition to psychosis in UHR. Several studies found that symptoms such as perceptual disturbances, unusual thought content, and ideas of reference are associated with later transition to psychosis (Cannon et al., 2008; Haroun et al., 2006). Two large studies of the North America Prodrome Longitudinal Study (NAPLS) (Cannon et al., 2008) and the Personal Assistance and Clinical Evaluation (PACE) study in Australia (Thompson et al., 2011) confirmed the high Positive Predictive Value (PPV) of subjects reporting high unusual thought content scores as well as low functioning and having genetic risk with functional decline. However, when examining symptom dimensions, using both the CAARMS and SOPS, there has been no link between positive symptoms and transition to psychosis (Demjaha et al., 2010; Fernández et al., 2006; Raballo et al., 2011).

Replicating the finding in psychosis (van Os et al., 1996), there have been several studies highlighting the importance of negative symptoms in the UHR population (Lencz et al., 2004), linking negative symptoms and transition to psychosis (Mason et al., 2004; Valmaggia et al., 2013; Velthorst et al., 2009; Yung et al., 2005) and finding persistency of negative symptoms even after treatment (Fusar-Poli et al., 2015; Piskulic et al., 2012). Again, replicating psychosis (Ortiz et al., 2015),

disorganised symptoms have been shown to predict transition in UHR (Lam et al., 2006; Mason et al., 2004; Riecher-Rössler et al., 2009).

Three of the four studies examining symptom dimensions in UHR (Demjaha et al., 2010; Fernández et al., 2006; Hawkins et al., 2004; Raballo et al., 2011) have used dimensions to determine risk of transition. Using the SIPS/SOPS Fernández et al. (2006) found that Negative and Disorganised dimensions had a 96.7% and 90% PPV respectively for transition to psychosis after 1 year, in a sample of 30 subjects of whom 8 made transition to psychosis. Using the CAARMS, Demjaha et al. (2010) confirmed this result using Cox Proportional Hazards Regression, finding both the negative (hazard ratio = 1.68, 95% confidence interval = 1.01 – 2.80, p = 0.044) and disorganised dimension (hazard ratio = 1.70, 95% confidence interval = 1.16 – 2.29, p = 0.005) were associated with increased risk of subsequent transition to psychosis (n = 122). This was confirmed, also using Cox Proportional Hazards Regression on dimensions determined from the CAARMS by Raballo (2011) for the disorganised dimension (hazard ratio = 1.43, 95% confidence interval = 1.03 – 2.18), however not for the negative dimension.

Symptom Dimensions and Functional Outcome:

As described above, there has been a shift in focus in more recent longitudinal studies of UHR, to move beyond the singular determination of outcome in terms of psychotic transition, to consider outcome in terms of functional disability. When determining outcome using functional criteria rather than transition to psychosis, several studies have found links between symptoms and functional outcome (Allen et al., 2015).

Schlosser et al. (2012) found that subjects presenting with lower severity of negative and affective symptoms at baseline were more likely to present with symptomatic and functional recovery after 2 years, and Lin et al. (2011) found that the presence of negative symptoms and neurocognitive decline at baseline, regardless of transition to psychosis, were associated with poor functional outcome in UHR, whereas positive symptoms and baseline GAF were not. Disorganised and negative symptoms have been consistently shown to predict functional outcome in UHR (B. A. Cornblatt et al., 2007; Fulford et al., 2013; Niendam et al., 2007; H. Takahashi et al., 2005) as well as after long term follow up of 6 years (Ziermans et al., 2014).

Of the four studies that examined symptom dimensions in UHR, both Demjaha et al. (2010) and Raballo et al. (2011) looked at functional disability at baseline and found that all factors were associated with worse functioning at presentation, however neither study went on to examine how the dimensions relate to functional outcome.

4.1.4 Aims and Objectives of this Study

This chapter will examine the relationship between the symptom dimensions described in chapter 2 and baseline demographic (age/gender) and clinical variables (Global Assessment of Functioning). The association between CAARMS intake group (APS/BLIP/Genetic Vulnerability) will also be examined to determine any symptomatic differentiation between the groups.

The relationship between baseline dimension scores and outcome at follow up will then be examined, using transition to psychosis and level of functioning as the two outcome measures. On the basis of data from previous studies (Demjaha et al., 2010; Raballo et al., 2011), I tested the hypothesis that high scores on the negative and the disorganised dimensions will be associated with poor outcomes.

4.2 Method

4.2.1 Sample

The total sample comprised of 509 individuals meeting the PACE criteria for Ultra High Risk for Psychosis (UHR), aged 18-35 recruited through three different studies conducted between 2008 and 2017. Fifty-five participants were recruited through an MRC-funded study at King's College London; ninety through a Wellcome Trust funded programme at King's College London (collected by the author); and three hundred and sixty four from an FP7 project funded by the European Union, involving sites in the UK, Netherlands, Austria, Switzerland, France, Spain, Turkey, Australia, Belgium, Germany and Brazil. A breakdown of the total sample by location is shown in the table below. All studies had National Research Ethics Service (NRES) approval and all participants gave written informed consent to participate.

Table 16: Geographical Composition of Sample

Study	Location	Number	Percentage of total Sample (by country)
MRC Study	UK - London - South London	55	48.9
Wellcome Study	UK - London - South London	49	
	UK - Cambridge	21	
	UK - London - West London	10	
EU Study	UK - London - South London	104	
	The Netherlands - Amsterdam	19	19.1
	The Netherlands - Den Haag	68	
	Austria - Vienna	7	1.3
	Switzerland - Basel	19	3.7
	Germany - Cologne	16	3.1
	Australia - Melbourne	25	4.9
	Denmark - Copenhagen	19	3.7
	France - Paris	17	3.3
	Spain - Barcelona	23	4.5
	Brazil - Sao Paulo	17	3.3

4.2.2 Eligibility Criteria

Participants were recruited from specialist early intervention services and assessed by researchers trained to administer the measures. The eligibility criteria were the same as those used for the sample in chapter 2; detailed criteria can be found in section 2.2.2.

4.2.3 Measures

The Comprehensive Assessment of At Risk Mental State (CAARMS):

UHR status was determined using the Comprehensive Assessment of At Risk Mental State (CAARMS). This is described in detail in section 2.2.3.

The CAARMS was conducted at both baseline and Follow up.

The Global Assessment of Function (GAF):

A standard method used to assess a patients' overall level of psychological, social, and occupational functioning (American Psychiatric Association, 2000) . Ratings are based on a 1–100 scale, with 100 representing an absence of symptoms and superior functioning. Guidelines for rating the GAF describe symptoms and levels of functioning in 10-point intervals:

- 100 – 91: No symptoms or superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities
- 90 – 81: Absent or minimal symptoms (e.g. mild anxiety before an exam, generally satisfied with life), no more than everyday problems or concerns (e.g. occasional arguments with family members). Good functioning in all areas, interested and involved in a wide range of activities, socially effective
- 80 – 71: If symptoms are present, they are transient and expectable reactions to psychological stressors (e.g. difficulty concentrating after

family argument). No more than slight impairment in social, occupational or school functioning (e.g. temporarily falling behind in school work)

- 70 -61: Some mild symptoms (e.g. depressed mood and mild insomnia). Some difficulty in social, occupational or school functioning (e.g. occasional truancy or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships
- 60 – 51: Moderate symptoms (e.g. flat affect and circumstantial speech, occasional panic attacks). Moderate difficulty in social, occupational or school functioning (e.g. few friends, conflicts with co-workers)
- 50 – 41: Serious symptoms (e.g. suicidal ideation, severe obsessional rituals, frequent shoplifting). Any serious impairment in social, occupational or school functioning (e.g. no friends, unable to keep a job)
- 40 – 31: Some impairment in reality testing, or communication (e.g. speech is at times illogical, obscure or irrelevant). Major impairment in several areas, such as work or school, family relations, judgement, thinking or mood (e.g. depressed man avoids friends, neglects family and is unable to work; child frequently beats up younger children, is defiant at home and is failing in school)
- 30 -21: Behaviour is considerably influenced by delusions or hallucinations. Serious impairment in communication or judgement (e.g. sometimes incoherent, acts grossly inappropriately, suicidal preoccupation). Inability to function in almost all areas (e.g. stays in bed all day, no job, home or friends)

- 20 -11: Some danger of hurting self or others (e.g. suicide attempts without clear expectation of death, frequently violent, Affective Instability excitement), gross impairment in communication (e.g. largely incoherent or mute). Occasionally fails to maintain minimal personal hygiene (e.g. smears faeces)
- 10 – 1: Persistent danger of severely hurting self or others (e.g. recurrent violence). Serious suicidal act with clear expectation of death. Persistent inability to maintain minimal personal hygiene

The GAF was implemented by a trained clinician and it was conducted at baseline and follow up. Two of the studies (92% of the sample) used a separate GAF – Symptoms and GAF – Disability rating scales, and the remaining study used only one overall rating.

4.2.4 Symptom Dimensions

The symptom dimensions were those determined in chapter 2. The dimensions and CAARMS items that load on them are shown in figure 4 in section 2.3.4.

4.2.5 Outcome Measures

Both the CAARMS and GAF assessments were conducted at 2-year follow up. CAARMS scores and clinical records were used to determine whether a subject had made a transition to psychosis. A severity score of 6, with frequency greater than 4 on any of the items in the Positive scale was classified as Psychotic. If CAARMS ratings were not available (e.g. because a subject did not participate in a follow up visit), transition to psychosis was determined on the basis of the diagnosis made by clinical services.

GAF scores were used to determine functional outcome. Subjects were divided into two functional outcome groups on the basis of their scores at 2 year follow-up:

1. Good functional outcome – defined as GAF score ≥ 65
2. Poor functional outcome – defined as GAF score ≤ 64

This approach follows that previously used in the study by (Allen et al., 2015). Scores in the 61–70 range are associated with "some difficulty in social, occupational or school functioning, but generally functioning pretty well".

4.2.6 Missing Data

Listwise deletion of missing data was used - cases are dropped from analysis if they have a missing value in at least one of the specified variables. A complete CAARMS baseline score for all items was needed to calculate total CAARMS score and scores for each dimension. After removal of subjects for whom there were missing data the sample size was 493. There were also several subjects who were included in more than one of the studies. Of an initial sample of 509, after removal of these subjects the sample size was 463. This is a larger total sample as the data extraction for this analysis was conducted three months later than the extraction for the analysis in chapter 2, during which time CAARMS data for two participants had been added.

4.2.7 Statistical analysis

As the data came from three different studies, an initial group comparison was performed to determine whether the respective data sets were sufficiently statistically similar to be pooled. This required that they have statistically similar

subjects by age and gender, and shared the same structure of CAARMS scores, which would be expected if they represented different samples of the same population.

Pearson product-moment correlation coefficient was used to determine which dimensions were associated with other baseline variables, grouped as sociodemographic and functional variables - age and GAF score. Chi square test was used to assess if any difference was present between the dimensions according to gender, and analysis of variance for comparisons of the total scores between inclusion groups.

Both previous studies (Demjaha et al., 2010; Raballo et al., 2011) used Cox Proportional Hazards Regression to examine the relationship between the derived factors and transition to psychosis/functional outcome, this is because both studies had not completed a two year period of observation to allow for valid determination of transition to psychosis (Fusar-Poli et al., 2012). This method is suitable for investigating the effect of variables upon the time a specified event takes to happen, and will therefore take in to account the continued risk of transition. As the follow up time period of over two years for this study, logistic regression will be used to determine the relationship between dimensions and outcome. This will determine the statistical likelihood of the outcome at two years, rather than an odds ratio of the event occurring over time.

4.3 Results

4.3.1 Test of Homogeneity

In order to combine the three data sets, a one way analysis of variance was conducted to compare means of age and gender between the groups and no significant differences were present (age: $t(2) = 2.528$, $p = 0.876$; gender: $t(2) = 0.019$, $p = 0.926$). Levene's test of homogeneity of variance was performed on the CAARMS scores for the three data sets. This indicated equal variances of Total CAARMS scores ($F = 1.65$, $p = 0.193$) between the three samples, which suggested that the data sets could be pooled.

4.3.2 Sample Characteristics

Demographic information:

The final pooled sample consisted of CAARMS scores for 463 participants. The sample was 55% male, the mean age was 22 years and 7 months, and 63% of the subjects were white, 18% black and 14% from other ethnic minorities. 86% of the sample met the inclusion criteria for Attenuated Psychotic Symptoms (APS), 7% Brief Limited Psychotic Period (BLIP) and 7% Genetic Vulnerability. Gender, age, ethnicity and CAARMS intake group breakdowns for each sample are show in the table 17 below.

Table 17: Characteristics of Three Samples, Total Sample and Split Sample

Sample Group		Wellcome Study	MRC Study	EU Study	Total Sample
Sample Size		90	55	364	509
Number included		85	50	328	463
Age	Mean	22.47	22.56	22.22	22.66
	SD	3.60	4.43	4.78	4.35
Gender (male)		48 (56%)	27 (54%)	171 (52%)	246 (53%)
Ethnicity	White	54 (64%)	28 (56%)	212 (65%)	294 (63%)
	BME	31 (36%)	22 (44%)	116 (35%)	169 (36%)
Intake Group	APS	79 (88%)	42 (84%)	281 (86%)	401 (86%)
	BLIP	6 (7%)	0 (0%)	21 (6%)	31 (7%)
	Genetic Vulnerability	5 (5%)	8 (16%)	26 (8%)	31 (7%)

CAARMS Scores:

Baseline CAARMS scores recorded in the total sample ranged from 0-6 for each item, and every item was present (scored above 0) in at least 10% of the sample. The mean total score was 40.39 (SD = 20.33). A breakdown of scores for each item is shown in table 18 below.

Table 18: Mean, Standard Deviation and Range of all CAARMS Item

CAARMS group	Number	CAARMS Item	Minimum	Maximum	Mean	SD
1. Positive Symptoms	1.1	Unusual thought content and non-bizarre ideas	0	6	2.50	1.641
	1.2	Perceptual abnormalities	0	6	2.59	1.847
	1.3	Disorganized speech	0	6	1.54	1.484
2. Cognitive Change Attention/Concentration	2.1	Subjective cognitive change	0	5	2.05	1.305
	2.2	Observed cognitive change	0	5	0.70	1.005
3. Emotional Disturbance	3.1	Subjective emotional disturbance	0	5	1.73	1.532
	3.2	Observed blunter affect	0	6	0.84	1.217
	3.3	Observed inappropriate affect	0	6	0.34	0.892
4. Negative Symptoms	4.1	Alogia	0	5	1.21	1.258
	4.2	Avolition/apathy	0	6	2.53	1.699
	4.3	Anhedonia	0	6	2.39	1.870
5. Behavioural Change	5.1	Social isolation	0	6	2.20	1.738
	5.2	Impaired role function	0	6	2.42	1.887
	5.3	Disorganizing/odd/stigmatising behaviour	0	5	0.56	1.071
	5.4	Aggression/dangerous behaviour	0	6	1.88	1.640
6. Motor/Physical Changes	6.1	Subjective complaints of impaired motor functioning	0	4	0.49	0.914
	6.2	Informant reported or observed changes in motor functioning	0	4	0.15	0.520
	6.3	Subjective complaints of impaired bodily sensation	0	6	0.63	1.253
	6.4	Subjective complaints of impaired autonomic functioning	0	5	0.85	1.332
7. General Psychopathology	7.1	Mania	0	6	0.61	1.218
	7.2	Depression	0	6	2.75	1.600
	7.3	Suicidality and self-harm	0	6	1.56	1.571
	7.4	Mood swings/lability	0	5	1.32	1.499
	7.5	Anxiety	0	6	2.67	1.716
	7.6	Obsessive compulsive symptoms	0	6	1.11	1.550
	7.7	Dissociative symptoms	0	6	0.98	1.494
	7.8	Impaired tolerance to normal stress	0	5	1.80	1.793
Total CAARMS Score			0	92	40.39	20.33

Two hundred and fifty two subjects (54%) of the sample completed the CAARMS at follow up. The average follow up time was 639 days (range 95 – 1002). The mean total CAARMS score at follow up was 34.46 (SD = 21.81). Of those who completed follow up CAARMS 39% were in symptomatic remission 49% still met APS Criteria, 2% met criteria for a BLIP and 9% had transitioned to psychosis. Of the total sample (including those who did not complete follow up CAARMS) fifty-one (11.8%) subjects made transition to psychosis in the two years from first contact (determined from clinical records for those who did not come in for follow up interview).

GAF Scores:

Four hundred and fifty eight subjects completed GAF at baseline (four hundred and eight of those had separate scores for symptoms and disability and the remaining fifty had only a total score). The mean symptom score was 59.31 (SD = 14.68, range = 15-100), the mean disability score was 69.82 (SD = 15.25, range = 30-100) and the mean total score was 59.16 (SD = 13.72, range = 30-100).

Two hundred and forty eight subjects completed GAF at follow up (two hundred and fourteen of those had separate scores for symptoms and disability and the remaining thirty four had only a total score). The mean symptom score was 63.05 (SD = 15.56, range = 15-100), the mean disability score was 63.94 (SD = 16.64, range = 15-100) and the mean total score was 62.32 (SD = 15.33, range = 15-100).

Symptom Dimensions:

Dimension scores were calculated as a mean of items that loaded on each factor as determined in the factor analysis in the second chapter. Information on baseline

CAARMS total scores and dimension scores are shown in table 19 below. Two hundred and fifty one subjects (54%) of the sample completed the CAARMS at follow up, follow up dimension scores are also shown in table 19.

Regression weights of the items on each factor (as determined by baseline CAARMS in chapter 2) are shown in figure 14 below. They all showed a loading of over 0.3, indicating reasonable fit.

Table 19: Descriptive Statistics of CAARMS Scores of 463 UHR subjects at baseline and 240 UHR subjects at Follow Up

		Baseline				Follow Up			
		Min	Max	Mean	SD	Min	Max	Mean	SD
CAARMS Total Score		0	92	40.39	20.33	0	91	31.32	21.81
Mean Dimension Scores (0-6)	Negative	0	5.25	2.34	1.41	0	5.00	1.85	1.39
	Disorganised - Behavioural	0	3.50	0.38	0.58	0	2.50	0.28	0.48
	Disorganised – Cognitive	0	4.00	1.37	0.91	0	5.00	1.07	0.94
	Affective Instability	0	4.67	1.14	0.99	0	4.33	1.02	0.94
	Anxiety	0	5.25	2.27	1.37	0	5.50	1.77	1.31

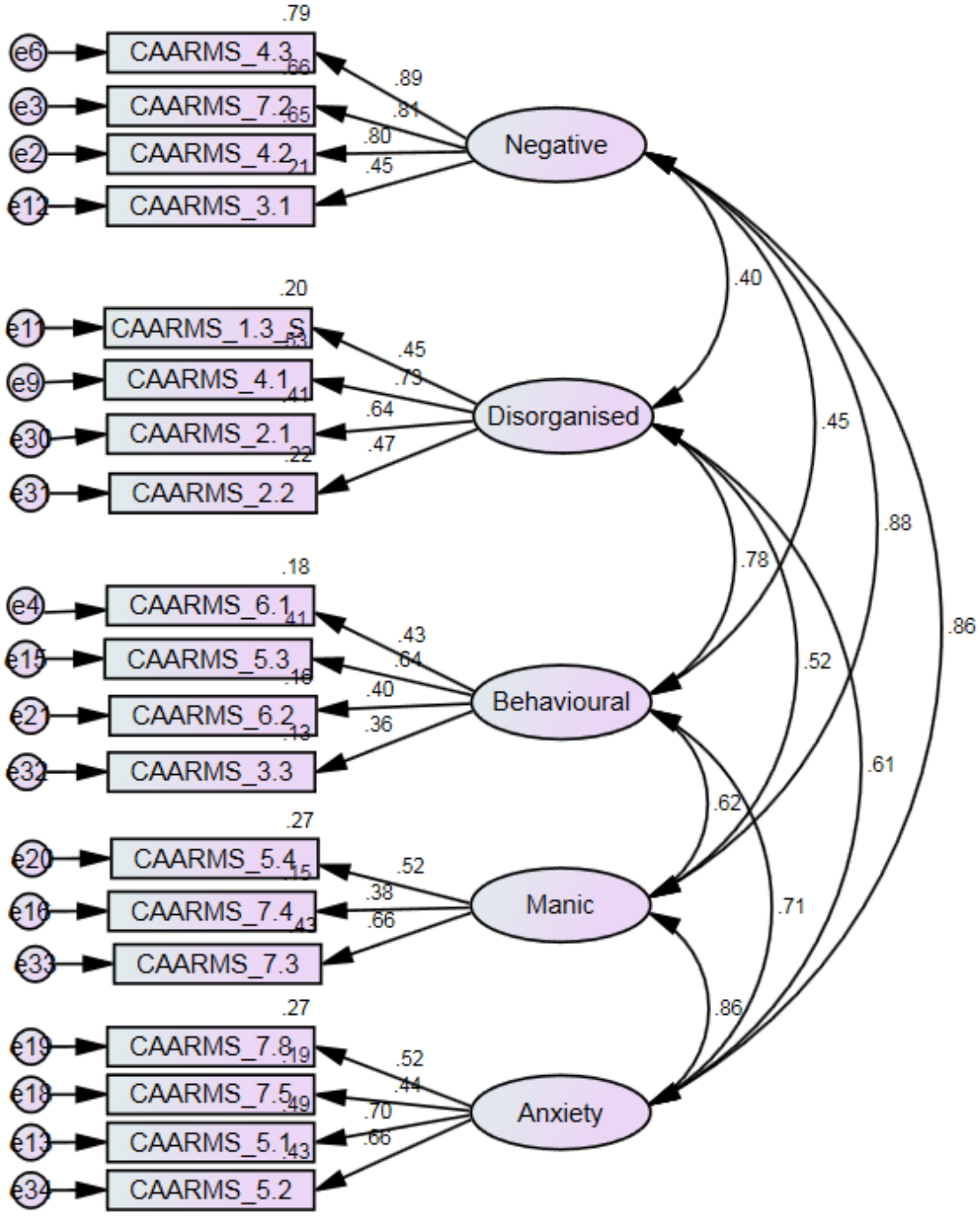

Figure 14: Standardised Regression Weights of Follow Up CAARMS for Dimensions determined by Baseline CAARMS

Characteristics of Patients not Followed Up:

Two hundred and fifty-two participants completed the full follow up interview, including the CAARMS and GAF. The mean duration of follow-up in this subgroup was 639 days (Median = 728 days, SD = 245 days). Two hundred and eleven subjects did not complete the follow up interview. In this subgroup, outcome data were obtained from clinical records. A comparison of the demographic and clinical characteristics in the two subgroups is shown below.

Table 20: Table showing the demographic characteristics of those who were followed up and those who were not

Sample Group		Total Baseline Sample	Followed Up	Not Followed Up
n		463	252	211
Age	Mean	22.66	24.25	24.63
	SD	4.351	4.516	4.839
Gender (male)		254 (55%)	137 (54%)	120 (56%)
Ethnicity	White	310 (67%)	173 (69%)	144 (68%)
	BME	153 (33%)	79 (31%)	67 (32%)
Intake Group	APS	398 (86%)	234 (93%)	178 (84%)
	BLIP	28 (7%)	8 (3%)	17 (8%)
	Genetic Vulnerability	32 (7%)	16 (6%)	16 (8%)
Baseline Dimension Scores - Mean (SD)	Negative	2.34 (1.41)	2.38 (1.40)	2.31 (1.42)
	Disorganised – Behavioural	0.38 (0.58)	0.41 (0.63)	0.35 (0.54)
	Disorganised – Cognitive	1.37 (0.91)	1.32 (0.91)	1.42 (0.90)
	Affective Instability	1.14 (0.99)	1.10 (1.00)	1.18 (0.98)
	Anxiety	2.27 (1.37)	2.26 (1.35)	2.27 (1.39)

A Chi Square test for association showed there was a significant difference in the intake group for those followed up and those not χ (2) = 6.182, p = .045. Those who completed follow up were more likely to have met APS CAARMS criteria but

less likely to have met BLIP criteria. There were no other significant differences between the two groups.

4.3.3 Baseline Correlates of Symptom Dimensions

Pearson product-moment correlation coefficient showed a positive correlation between age and the Affective Instability dimension, which was statistically significant ($r = -0.154$, $p = .001$) despite the correlation coefficient being small. There was no correlation between any of the other dimensions and age. An independent samples t-test showed that there was a significant difference between males and females for the Anxiety and Negative dimensions, with females scoring higher on both Negative (male: 2.20 ± 1.47; female: 2.47 ± 1.36; $t(447) = -2.032$, $p = 0.043$) and anxiety (male: 2.08 ± 1.41; female 2.43 ± 1.31; $t(447) = -2.720$, $p = 0.007$) dimensions. There was no significant difference between any of the other factors according to gender.

For all of the dimensions, a high score was correlated with a lower total GAF at baseline (Table 21 below). The strongest (negative) correlation ($r = -0.600$, $p = .000$) was between the scores on the Negative dimension and the GAF, which was considerably stronger than the correlation between Total CAARMS score and GAF ($r = -0.479$).

Table 21: Pearson's Correlation of Symptom Dimensions and Baseline Total GAF score

Factor	Negative	Disorganised - Behavioural	Disorganised - Cognitive	Affective Instability	Anxiety	Total CAARMS Score
Pearson Correlation	-.600	-.319	-.495	-.486	-.595	-.479
Sig. (2-tailed)	0.000	0.000	0.000	0.000	0.000	0.000

One-way ANOVA revealed a significant difference across the Inclusion groups (APS/BLIP/Genetic Vulnerability) for the Negative ($F(2, 409) = 3.091$, $p = .047$); Anxiety ($F(2, 409) = 6.169$, $p = .002$) and Disorganised - Cognitive ($F(2, 409) = 7.052$, $p = .001$) dimensions. Post hoc Tukey tests indicated that this reflected the APS group having higher mean scores on both the Negative (2.64 ± 1.25; 2.08 ± 1.38; $p = .05$) and the Anxiety dimensions (2.56 ± 1.21; 1.78 ± 1.15; $p = .003$) than the Genetic Vulnerability group, and the APS group having a higher mean score on the Disorganised - Cognitive dimension than the BLIP group (1.58 ± 0.83; 1.04 ± 0.89; $p = .005$). There was no statistically significant difference between the inclusion groups on the Affective Instability ($p = .194$) and Disorganised – Behavioural ($p = .278$) dimensions. The mean scores for each dimension in each

inclusion group are shown in figure 15 below. Multinomial logistic regression of the five factors showed that none of the five factors determined inclusion group.

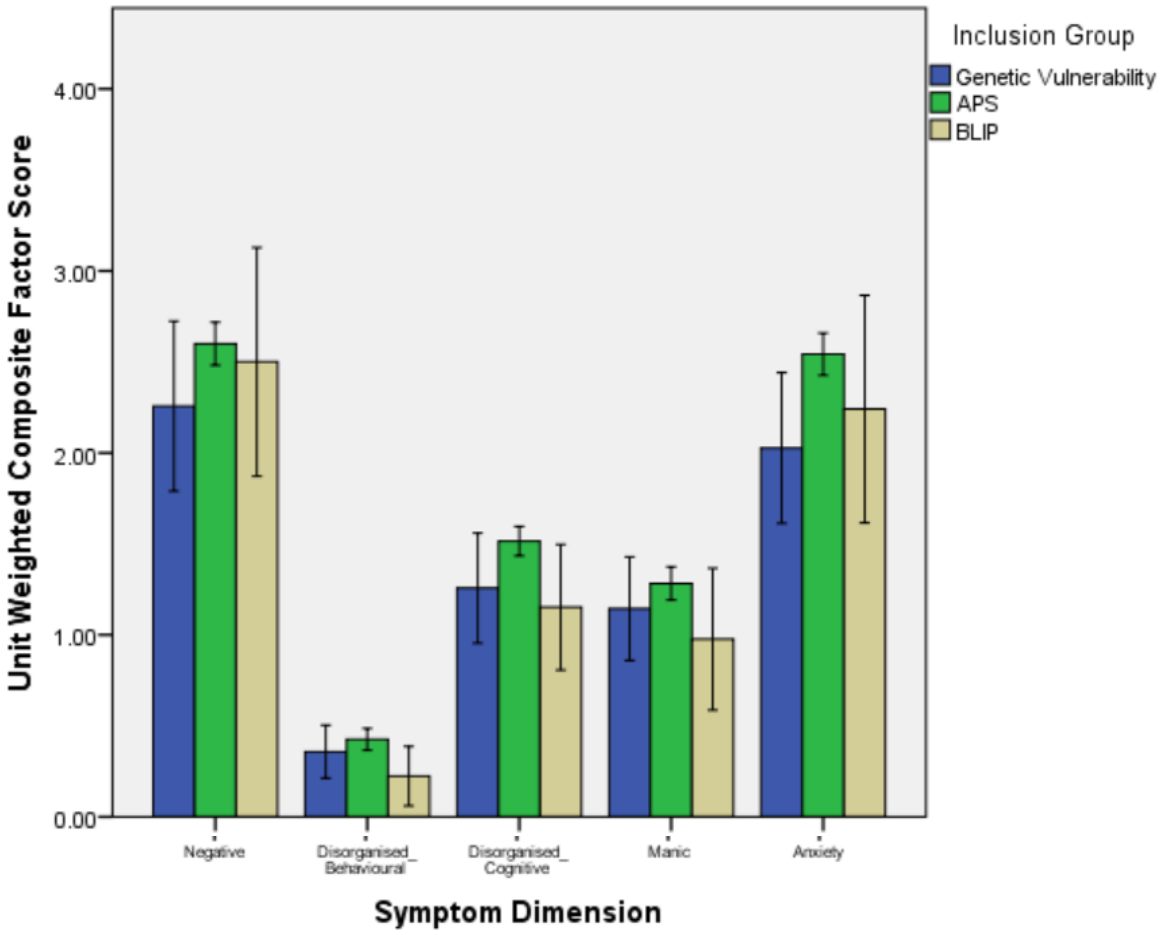

Figure 15: Bar Chart showing Unit Weighted Composite Factor Scores for each Dimension by Inclusion Group

4.3.4 Symptom Dimensions and Clinical Outcome

Transition to Psychosis:

Participants were followed up 24 months after baseline to assess whether psychosis had occurred. The mean duration of follow-up was 639 days (median = 728 days, SD = 245 days).

59 participants (11.8%) converted to psychosis during the follow up period. The mean number of days from baseline to transition to psychosis was 322 days (range: 5-1109). Of the subjects who transitioned, 59% were male and their average age at baseline was 22.2 years. Chi squared tests showed that there was no significant difference in age, gender or ethnicity between those who transitioned and those who did not.

An independent samples t-test examining differences in the five baseline dimensions scores and total CAARMS score of those who transitioned and those who did not showed that subjects who transitioned scored significantly higher in the CAARMS severity overall (transition: 49.74 ± 15.51; non-transition: 43.02 ± 16.83; $t(490) = -2.904$, $p = 0.004$) and on the Anxiety dimension than those who did not (transition: 11.56 ± 4.76; non-transition: 9.68 ± 4.98; $t(485) = -2.722$, $p = 0.007$).

Independent logistic regressions with age and gender as covariates for scores on each dimension and the total CAARMS score showed that scores on the Anxiety and the Affective Instability dimensions as well as the total CAARMS score were associated with an increased rate of transition to psychosis. In each case, subjects who made a transition scored higher at baseline than those who did not become

psychotic. The effects for the Anxiety dimension and the total CAARMS score were stronger than for the Affective Instability dimension. There were no significant differences between these those who did and did not transition to psychosis for scores on the other three dimensions. Results are shown in table 22 below.

Table 22: Table to show Separate Regression Analyses (P values) for Each of the Five Dimensions (Predictor Variables) and Transition to Psychosis

Factor	B	SE B	Wald	p	Exp (B)	95% C.I.for EXP(B) Lower	95% C.I.for EXP(B) Upper
Negative	0.053	0.029	3.413	0.065	1.055	0.997	1.116
Disorganised - Behavioural	0.094	0.052	3.276	0.070	1.099	0.992	1.217
Disorganised - Cognitive	0.067	0.042	2.532	0.112	1.070	0.985	1.162
Affective Instability	0.097	0.048	4.002	**0.045****	1.102	1.002	1.212
Anxiety	0.081	0.030	7.306	**0.007****	1.085	1.023	1.150
Total CAARMS Score	0.026	0.009	8.642	**0.003****	1.027	1.009	1.045

** Indicates p < 0.05

Functional Outcome:

The mean total GAF score at follow up was 62.32 (SD = 15.33, range = 15-100). One hundred and fifty three (56.5%) of those who completed GAF at follow up were defined as having a poor functional outcome (GAF < 65). Subjects who had a poor functional outcome had an average age of 22.4 years and were 54% male; Chi squared test showed no significant difference in age, gender or ethnicity between those who had a poor functional outcome and those who did not.

Of the 41 transitioned subjects who completed follow up GAF, 35 (85%) had poor functional outcome but 6 had a good functional outcome. However, in these 6 subjects there was a relatively long delay between the date of transition and the follow up GAF assessment: 163 days, as opposed to 48 days in the transition subjects with a poor functional outcome.

An independent samples t-test comparing the dimensions scores at baseline in those with a poor and a good functional outcome at follow up showed that the former subgroup had significantly higher scores on all five dimensions.

Table 23: Table to show the Difference Between Baseline Composite Symptom Dimension Scores in Good and Poor Outcome

Dimension	Functional Outcome	Mean	SD	t	df	p	95% C.I. Lower	95% C.I Upper
Negative	Good	10.02	4.99	5.74	249.00	0.000	2.45	5.01
	Poor	6.29	5.25	5.71	228.61	0.000	2.44	5.02
Disorganised - Behavioural	Good	1.96	2.46	6.25	248.00	0.000	1.07	2.05
	Poor	0.40	0.99	6.82	191.60	0.000	1.11	2.01
Disorganised - Cognitive	Good	5.50	3.68	4.61	254.00	0.000	1.14	2.83
	Poor	3.51	3.06	4.71	253.30	0.000	1.15	2.81
Affective Instability	Good	4.13	2.93	7.52	249.00	0.000	1.80	3.07
	Poor	1.69	1.94	7.89	243.05	0.000	1.83	3.04
Anxiety	Good	10.23	4.57	9.81	249.00	0.000	4.36	6.56
	Poor	4.77	4.12	9.94	243.76	0.000	4.38	6.54

Independent logistic regressions with age and gender as covariates for each dimension and the total CAARMS score revealed that the Disorganised – Behavioural dimension was associated with an increased risk of a poor functional outcome: subjects with a poor functional outcome scored higher on this dimension than those with a good outcome. In this analysis there were no significant differences in relation to functional outcome on the other four dimensions. Results are shown in table 24 below

Table 24: Table to show Separate Regression Analyses (P values) for Each of the Five Dimensions (Predictor Variables) and Transition to Psychosis

Factor	B	SE B	Wald	Sig.	Exp (B)	95% C.I.for EXP(B) Lower	95% C.I.for EXP(B) Upper
Negative	-0.014	0.025	0.310	0.578	0.986	0.939	1.036
Disorganised - Behavioural	-0.136	0.061	4.895	**0.027****	0.873	0.774	0.985
Disorganised - Cognitive	-0.041	0.040	1.058	0.304	0.960	0.888	1.038
Affective Instability	-0.059	0.046	1.665	0.197	0.942	0.861	1.031
Anxiety	-0.041	0.027	2.301	0.129	0.960	0.910	1.012
Total CAARMS Score	-0.012	0.008	2.463	0.117	0.988	0.972	1.003

** Indicates p < 0.05

4.4 Discussion

4.4.1 Aims and Results of the Study

At baseline, higher severity scores on all five factors were associated with a lower level of functioning, with scores on the Negative dimension being most strongly correlated with lower functioning. Although there were significant differences between scores on the Negative, Disorganised and Affective Instability dimensions between inclusion groups for the UHR state, none of the dimensions determined inclusion group.

After an average of 1 year and 9 months of follow up, 51 subjects (12%) in this sample had transitioned to psychosis. The regression analyses of follow up data showed that scores on the Anxiety dimension and the total CAARMS score, and to a lesser extent the Affective Instability dimension predicted later transition to psychosis. Scores on the Disorganised - Behavioural dimension predicted a poor functional outcome, independent of whether a subject became psychotic or not.

4.4.2 Comparison with Previous Studies

Both Demjaha et al. (2010) and Raballo (2011) found strong links between a negative dimension and later transition to psychosis, which was not the case in this sample. This is also in direct contrast to findings in schizophrenia, where a negative dimension has consistently been linked to a worse clinical outcome (Levine & Leucht, 2013; Rabinowitz et al., 2012; van Os et al., 1996). This apparent discrepancy may be because two items (Impaired Role Function and Social Isolation) that were included in the negative dimension in both the Demjaha and the Raballo models (in figures 1 and 2 in section 2.1.3 and 2.1.4 respectively) were

included in the Anxiety dimension in the current model (shown in figure 4 in section 2.3.4. A detailed comparison of the three models is in section 2.4.2).

A link between anxiety items and Impaired Role Function and Social Isolation is not unexpected. In the Raballo model all these items loaded on their Negative/Interpersonal dimension and it was this dimension, including both negative and anxiety symptoms that was linked to transition. Anxiety symptoms in UHR subjects have also been linked to a poor functional outcome (Fusar-Poli et al., 2014).

The deficits in emotional and executive functioning that are widely reported in anxiety disorders (Sylvester et al., 2012) are also significant impairments in patients with schizophrenia (Minzenberg et al., 2009; Tseng et al., 2016), therefore it may be that these symptoms in UHR are critical in determining the risk of transition to psychosis, rather than specifically the anxiety symptoms. A breakdown of the link between each of the four items (Anxiety, Impaired Role Function, Impaired Tolerance to Normal Stress and Social Isolation) included in the Anxiety dimension and their relationship to transition would determine this.

The finding that Affective Instability symptoms (Mood Swings, Aggression and Dangerous Behaviour and Suicidality and Self Harm) were associated with later transition to psychosis has not previously been found. It may be that these symptoms are not indicative of transition in themselves, but that they are symptoms that arise in response to the presence of severe positive symptoms (that did not load on any factor, so are not included). This is supported by the finding that higher total CAARMS score, which includes all the positive item scales,

predicts transition. In general, the finding that increased severity of baseline presentation indicates an increased risk of transition to psychosis is in line with expectations and has been found in several UHR studies (Cannon et al., 2008; Ruhrmann et al., 2003; Valmaggia et al., 2013; Yung et al., 2005).

At baseline, all symptom dimensions were linked to lower functioning, a finding in line with those from both previous UHR studies (Demjaha et al., 2010; Raballo, 2011). However, previous studies did not look at the relationship between baseline dimension scores and level of functioning at follow up. My finding that the Disorganised – Behavioural dimension was linked to poor functional outcome is consistent with findings in patients with psychosis (Fulford et al., 2013; O'Leary et al., 2000; Ortiz et al., 2015) reporting disorganised symptoms are associated with repeated admissions and poor social and role functioning. The link between disorganised symptoms and poor functional outcome has also been found in several previous studies of UHR subjects (Carrión et al., 2013; Niendam et al., 2007; Ziermans et al., 2014).

However, in the present study it was the Disorganised - Behavioural dimension that was associated with poor functional outcome, as opposed to the Disorganised – Cognitive dimension. Several previous studies have found a link between neurocognitive functioning and functional outcome in the UHR group (Lin et al., 2011; Niendam et al., 2007). This differentiation between cognitive and behavioural disorganisation may mirror the distinction made by B. A. Cornblatt et al. (2007) between social and role function in the NAPLS study, who argued that these represent two distinct domains that need to be disentangled to avoid

confounding functioning with psychiatric symptoms. When measuring functioning in terms of social (appropriate relationships and social interaction) and role (performance and cognitive ability) functioning, B. A. Cornblatt et al. (2007) found that impairments in social functioning were relatively stable and were associated with later transition, whereas impaired role functioning became worse in the lead up to presentation but then improved during clinical follow up. This finding has been replicated by Velthorst et al. (2010), and is in line with poor outcome being linked to behavioural (social) disorganisation rather than cognitive (role) disorganisation.

4.4.3 Limitations

Although at baseline there were no significant demographic or clinical differences between subjects who completed follow up and subjects who did not, differences in functioning at the time of follow up could have influenced the results. Subjects with relatively poor functioning may be less likely to attend a follow up interview. Therefore the follow up information may not be representative of the entire population after two years.

Binary logistic regression was used in this analysis to determine the relationship with outcome, however, this uses a fixed time point to determine outcome. As determined by Fusar-Poli et al. (2012), a small proportion of UHR subjects may develop psychosis more than two years after presentation. It is thus possible that further subjects in the present sample will go on to become psychotic, and this might alter the findings. It may also have contributed to the transition rate (11%) being relatively low (see general discussion). The majority of subjects in the

present study were recruited through clinical services, so it should be possible to obtain information on clinical outcomes beyond the two year follow up period, even though the original research studies have now been completed.

The low transition rate could be due to: a) incomplete follow up – only 2 years b) selection bias whereby more severely ill / impaired UHR subjects decline to take part in intensive and demanding research projects. For Example: EU-GEI entailed multiple and lengthy assessment interviews, while other projects involved multi-modal neuroimaging. C) referral bias – as clinical services for UHR become well known, the typeof UHR person referred may change, such that less obviously ill / impaired individuals are referred. (Fusar-Poli et al, 2017)]

4.4.4 Future Research Directions

The distinction of outcome according to function is an important step in considering the risk in the UHR population not only as transition to psychosis. By doing so we are categorising all those who do not transition in to one outcome group, whereas the functional outcome considers the effect on personal, social and employment outcomes. However, there are several more considerations that would be interesting to investigate. For this study, we determined outcome in terms of binary functionality, however, it would be valuable to include comorbid diagnosis to differentiate this (Meyer et al., 2005). Future studies could attempt to further distinguish the sample according to presence of comorbidity, both when linking baseline predictors to functional outcomes and also when considering diagnostic outcome. It would also be interesting to discover, as has been shown by

Schlosser et al. (2012), whether there are any symptomatic predictors of remission.

This study has begun to examine the phenomenology of symptoms in UHR and how it differs from psychosis, however there are many more considerations, in terms of baseline and outcome variables, that would add to the model and refine its structure and application.

5 General Discussion

5.1 Summary of Main Findings

5.1.1 Factor Structure

An exploratory factor analysis identified a 5-factor structure that fitted the data, including 19 of the 27 CAARMS items, in a sample of 461 subjects at UHR of psychosis from multiple sites. Confirmatory factor analysis compared this model with those previously described in the literature, and found it to be the best fit in an independent data set.

The five dimensions were:

- Negative
- Disorganised – Behavioural
- Disorganised – Cognitive
- Anxiety
- Affective Instability

5.1.2 Symptom Dimensions and rCBF

ASL was used to examine the relationship between rCBF and severity scores for each dimension and total CAARMS scores. In the subsample of subjects who were scanned and had usable data (n=70), ROI analysis of the areas previously found by Allen et al. (2016) the left hippocampus, left pallidum and left midbrain. ROI analysis of Negative dimension scores did not show any correlation between negative dimension scores in the areas specified by Pinkham et al. (2011),

however there were significant reductions in CBF in one of the areas identified by P. F. Liddle et al. (1992): mediodorsal thalamus and the Disorganised – Behavioural dimension. Whole Brain analysis showed decreased perfusion in the scores on the Disorganised – Behavioural factor were found to correlate with a significant reduction in rCBF in the left hippocampus and the thalamus bilaterally. Scores on the Anxiety dimension were correlated with significant reductions in rCBF in bilateral prefrontal and cingulate cortex.

5.1.3 Symptom Dimensions and Clinical Presentation and Outcome

Higher scores on all dimensions were associated with worse functional presentation at baseline. The analysis of the relationship between factor scores and transition to psychosis showed that higher scores on the Anxiety and Affective Instability dimension and higher total CAARMS score were associated with increased risk of transition to psychosis, and higher scores on the Disorganised – Behavioural dimension was associated with worse functional outcome at 21 month follow up.

5.2 Discussion

The poor social and economic outcome, functional impairments and health and societal costs of psychotic disorders (Boonstra et al., 2012), have led to an increasing focus on early clinical detection and intervention. The UHR state is a clinical syndrome that is associated with a very high risk of developing psychosis. However, the majority of UHR subjects do not go on to develop a psychotic disorder (Fusar-Poli et al., 2012) and a significant proportion have substantial clinical needs even if they do not become psychotic (Fusar-Poli et al., 2014). The

most recent Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) has included 'attenuated psychosis syndrome' in its Appendix (Section III) as a disorder that merits further study. Attenuated psychosis syndrome, however is not determined solely in terms of risk of transition to psychosis; it is rather defined as 'a currently relevant clinical condition leading to help seeking, with many more clinical outcomes other than conversion to psychosis.' Given the diversity of clinical outcomes in the UHR group, it is may be helpful to consider their clinical presentation in terms of symptom dimensions, which are independent of diagnostic categories.

This study indicates that there are five distinct dimensions of symptoms measured by the CAARMS. Two previous studies looked at the dimensional structure of symptoms in the UHR using the SOPS (Comparelli et al., 2011; Hawkins et al., 2004). Both identified a three factor structure roughly comprising Positive, Negative and Disorganised symptoms, (n = 128 and n = 49 respectively). However, a study conducted concurrently with this one, also in a large UHR sample (n=334) and using PAF with an oblique rotation, reported that a four factor structure fitted the data better, with the items that were previously grouped on to one dimension in the three factor models, splitting exactly in to two separate dimensions (Tso et al., 2017). Using Principle Axis Factoring this study found four latent factors explaining 36.1% of the total variance: positive symptoms; distress; negative symptoms; and deteriorated thought process. The sample in this study was younger (age range: 12-25, mean: 17) and included both high and low clinical risk as well as very early first episode psychosis.

This pattern of the large dimensions splitting in to two underlying ones has also been found in the present study using the CAARMS, with the five factor structure very similar to Demjaha et al. (2010), and almost exactly splitting two of the three factors found by Raballo et al. (2011) each in to two separate factors demonstrated in figures 16 and 17. This may be because a larger sample allows the distinctions between the two underlying factors to become more distinct, whereas in a smaller sample the limited variation does not allow for them to be distinguished.

Current Model	CAARMS Item	Raballo Model
	3.2 OBSERVED BLUNTER AFFECT	Disorganised
Disorganised - Cognitive	1.3 DISORGANISED SPEECH 2.2 OBSERVED COGNITIVE CHANGE 2.1 SUBJECTIVE COGNITIVE CHANGE 4.1 ALOGIA	
	7.1 MANIA	
Disorganised - Behavioural	7.7 DISSOCIATIVE SYMPTOMS 5.3 DISORGANISING/ODD BEHAVIOUR 6.2 INFORMANT REPORTED OR OBSERVED CHANGES IN MOTOR FUNCTIONING 6.1 SUBJECTIVE COMPLAINTS OF IMPAIRED MOTOR FUNCTIONING 3.3 OBSERVED INAPPROPRIATE AFFECT	
	3.1 SUBJECTIVE EMOTIONAL DISTURBANCE 1.1 UNUSUAL THOUGHT CONTENT AND NON BIZARRE IDEAS	

Figure 16: Figure to Show Comparison of Disorganised Dimensions of Raballo Model and Current Model

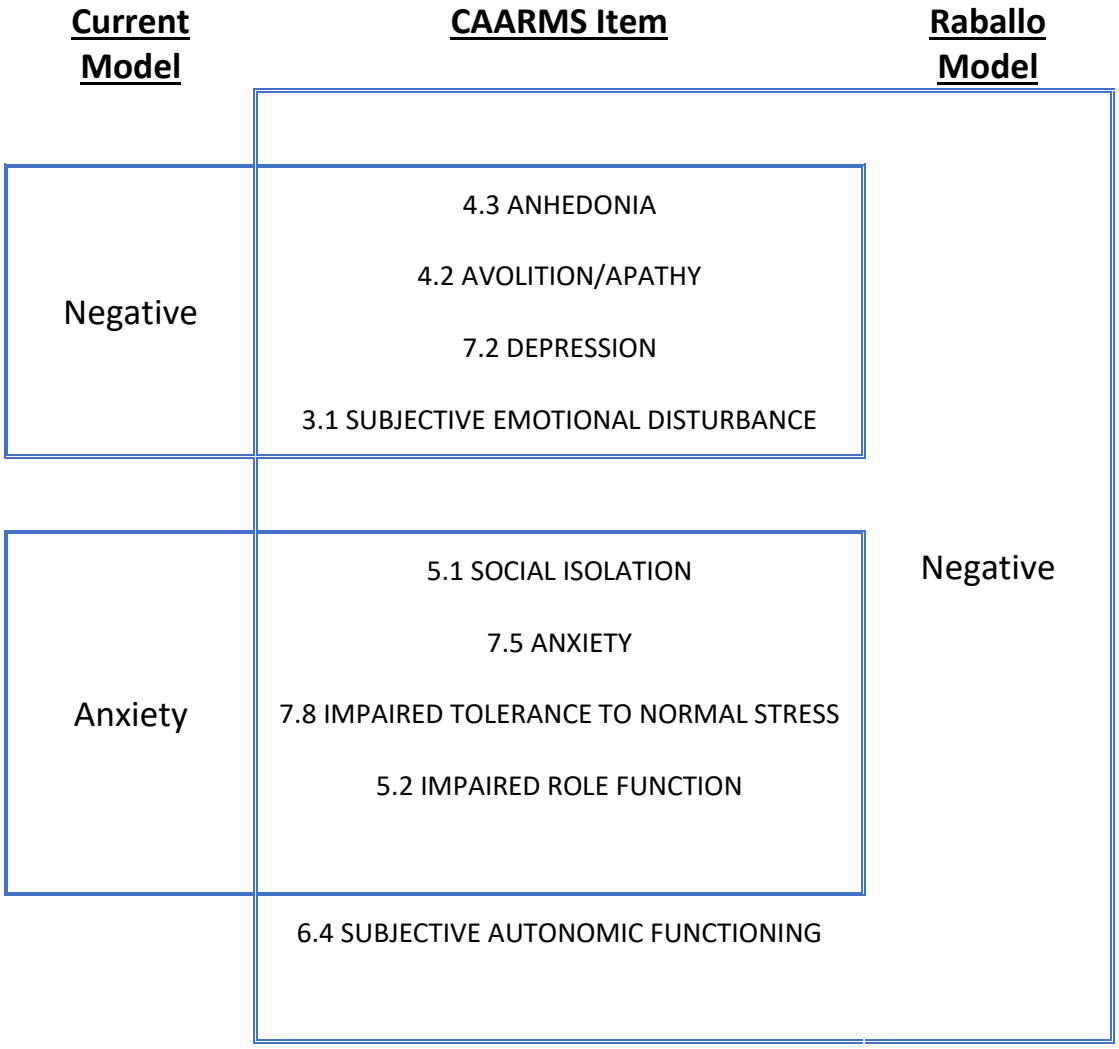

Figure 17: Figure to Show Comparison of Negative Dimensions of Raballo Model and Current Model

This finding of larger dimensions splitting in to two smaller ones in both CAARMS and SOPS may suggest a hierarchical factor structure. This was initially suggested by M. J. Cuesta and Peralta (2001) and confirmed in First Episode psychosis by Russo et al. (2014) where factor analyses identified 6 first-order factors (mania, negative, disorganization, depression, hallucinations, and delusions) and 2 high-order factors (affective and non-affective psychoses).

Furthermore, this thesis suggests that symptom dimensions in the UHR state may have distinct neural correlates. Although this has previously been described for symptom dimensions in schizophrenia (Liddle et al., 1992), this is the first evidence that this may also be true of the UHR state. Although the sample in the present study was relatively large for a neuroimaging study, the findings require replication, ideally in even larger UHR samples.

The finding that scores on symptom dimensions may be related to the risk of later transition to psychosis and functional outcome is of great interest, as it raises the possibility that measures of dimensions could ultimately be useful in clinical tools that are designed to predict the risk of psychosis. Such tools are still in their infancy, and it is unclear which types of baseline measures (clinical, cognitive, genomic, neuroimaging) will be most useful as predictors in a clinical setting (McGuire et al., 2015).

Further research in this area could build on the outcomes examined here to determine whether any particular dimension scores at baseline predicted remission from UHR state as opposed to persistent UHR symptoms, or whether baseline dimensions predicted the type of psychosis that developed (e.g.: Affective

Instability –bipolar; Negative –schizophrenia); or the development of other mental health diagnoses.

A possible application of symptom dimension scores in the UHR group is that these could provide a guide to the most appropriate form of clinical intervention. For example, there is some evidence that in psychosis patients, Cognitive Remediation has a selective effect on scores on disorganised and negative dimensions (Cella et al., 2014).

The finding that the anxiety dimension predicts transition is of clinical relevance as Cognitive Behavioural Therapy (CBT) for anxiety could be used instead of CBT for psychosis – which has questionable efficacy. In a systematic review and meta-analysis of the effectiveness of CBT for schizophrenic symptoms Jauhar et al. (2014) found that CBT has a low therapeutic effect on schizophrenic symptoms which reduces further when sources of bias, particularly masking, are controlled for.

Two meta-analyses examining intervention in the UHR group have found low (Marshall & Rathbone, 2011) to moderate (Stafford et al., 2013) effects of intervention at this stage, indicating that a more specialised focus is needed to target lower transition rate and better functional outcome.

The key role of the Anxiety factor in determining transition is an interesting finding in UHR, since previous studies have highlighted the importance of negative symptoms (Valmaggia et al., 2013). Anxiety is known to affect emotional regulation and attentional control and wide ranging impairments in emotional and

executive functioning are evident in schizophrenia (Minzenberg et al., 2009). In the Tso et al. (2017) SOPS model, this is also reflected with the distress factor accounting for a larger proportion of the variance than the negative or disorganised factors, and confirms the importance of anxiety and mood symptoms highlighted in many recent studies (Fulford et al., 2013; Lin et al., 2015; Rietdijk et al., 2013).These findings suggest that the young people at UHR of psychosis may resemble an affectively disturbed group (A. P. Morrison et al., 2012) which has clinical implications for assessment, intervention, and treatment. Rather than a specific focus on positive symptoms of psychosis, this study highlights the importance of intervention aimed at treating affective dysregulation, which may in turn affect the rate of transition.

The transition rate in this large sample was 11% at two years, which is significantly lower than the 29% determined in the meta-analysis by Fusar-Poli et al. (2012). This may be due to the increasing clinical focus on early detection of UHR subjects, such that more recent studies are recruiting individuals at an earlier stage or who are less severely ill than in previous studies. Clinical UHR services may now be more likely to provide active clinical intervention, as opposed to passive monitoring. In a recent analysis of transition rates Nelson et al. (2016) found that patients with a short duration of UHR symptoms had lower transition rates. It may also be due to a selection bias – the interview for participating in the studies used was up to three hours long and included multimodal imaging. More severely ill patients may not have agreed to this long process or may not have been able to complete it. The rate of 11% in this study is in line with more recent studies in

London (Allen et al., 2015; Allen et al., 2016) as well as elsewhere (A. P. Morrison et al., 2012; Velthorst et al., 2009).

5.3 Limitations

Specific limitations for each experimental chapter are considered in their respective sections; however, there is one overarching limitation to be considered when working with UHR cohorts. Due to the non-specific nature of prodromal symptoms, there are reasonable concerns about premature labelling as clinical features can be difficult to distinguish from benign conditions and normal experience. This is why research in this population needs to be cognisant of the 'false positive' group, and why determination of outcomes other than transition to psychosis need to be considered.

This study also uses the UHR group as a whole, including participants who meet all three inclusion groups: APS, BLIP and Genetic Vulnerability (as has been the case in the previous CAARMS and SOPS factor analyses). There has been recent discussion of whether it makes clinical sense to combine the three groups after studies such as P Fusar-Poli et al. (2016a) found differing risk of transition in the BLIP group compared to APS and Genetic Vulnerability, APS alone and Genetic Vulnerability alone groups. Although the APS group makes up the majority of the sample (86%), the clinical and symptomatic presentation across the groups vary, and therefore it would interesting to investigate or confirm the factor structure in a more homogeneous group of APS only.

5.4 Conclusions

One of the fundamental goals in understanding the Ultra High Risk state is linking the observable symptoms to the underlying unobservable pathophysiology, and discerning their clinical relevance. This study shows that a dimensional approach to psychopathology may facilitate the assessment of the clinical heterogeneity of this population and their underlying distinct neurobiology. It also shows that presenting symptomatology can be characterised by dimensions that have distinct associations with outcome, whilst highlighting the importance of continued research to inform the understanding of the development of psychosis and the functional impairments associated with the UHR state.

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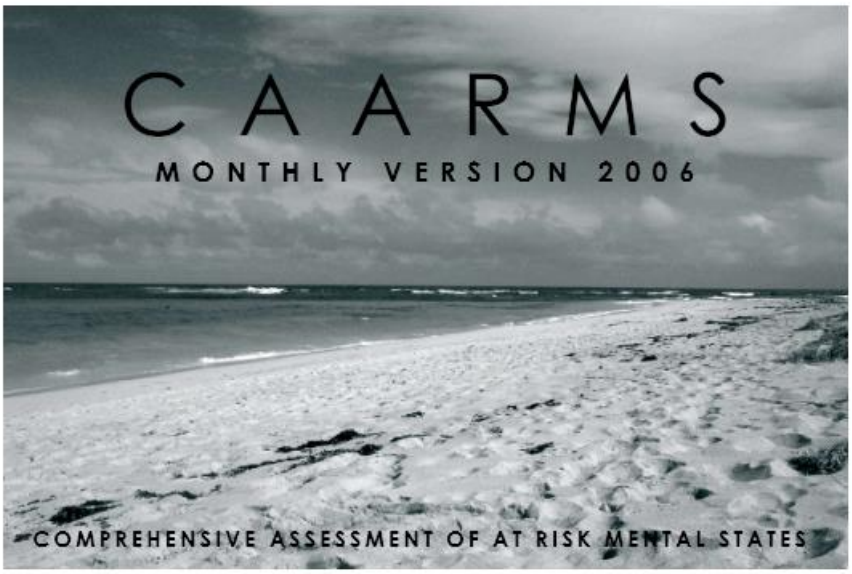
7 Appendices

7.1 Appendix 1: Comprehensive Assessment of At Risk Mental State



A. Yung, L. Phillips, M.B. Simmons, J. Ward, K. Thompson, P. French, P. McGorry

Name: _____

Date: _____ / _____ / _____

CRF #: _____

Rater: _____

The PACE Clinic
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Melbourne, Australia

OVERVIEW OF THE CAARMS

Aims:

- To determine if an individual meets the criteria for an 'At Risk Mental State'.
- To rule out, or confirm criteria for acute psychosis.
- To map a range of psychopathology and functioning factors, over time in young people at ultra high-risk of psychosis.

Structure of the CAARMS:

- Ratings are made on a range of subscales that target different areas of psychopathology and functioning. From these ratings it is then possible to extract information relating to the above aims.

Overview of Symptoms and Functioning - Longitudinal Change:

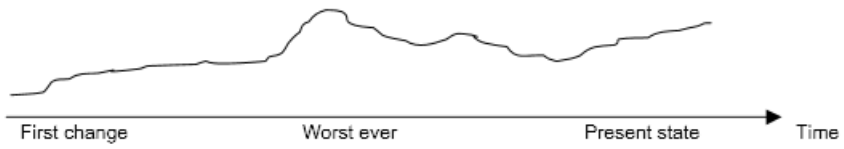
- At the first interview (not follow-up interviews), the CAARMS aims to obtain a general overview of the history of change from the premorbid state in the respondent. All available information should be used.
- Record the **time of first noted change** - date and age of respondent in years:

  Date: .....
  Age: .....

- Note first ever symptoms or signs:

  .....
  .....
  .....
  .....
  .....

- Overview of course since then - map on timeline e.g.:



- Current time line:

INDEX

1: Positive Symptoms

1.1 Unusual Thought Content

Delusional Mood and Perplexity ('Non Crystallized Ideas')

- Have you had the feeling that something odd is going on that you can't explain? What is it like?
- Do you feel puzzled by anything? Do familiar surroundings feel strange?
- Do you feel that you have changed in some way?
- Do you feel that others, or the world, have changed in some way?

Ideas of Reference

- Ideas of Reference: Have you felt that things that were happening around you had a special meaning, or that people were trying to give you messages? What is it like? How did it start?

Bizarre Ideas ('Crystallized Ideas')

- Made thoughts, feelings, impulses: Have you felt that someone, or something, outside yourself has been controlling your thoughts, feelings, actions or urges? Have you had feelings or impulses that don't seem to come from yourself?
- Somatic Passivity: Do you get any strange sensations in your body? Do you know what causes them? Could it be due to other people or forces outside yourself?
- Thought Insertion: Have you felt that ideas or thoughts that are not your own have been put into your head? How do you know they are not your own? Where do they come from?
- Thought Withdrawal: Have you ever felt that ideas or thoughts are being taken out of your head? How does that happen?
- Thought Broadcasting: Are your thoughts broadcast so that other people know what you are thinking?
- Thoughts Being Read: Can other people read your mind?

UNUSUAL THOUGHT CONTENT- NLOBAL RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Psychotic and Severe**
No unusual thought content.	Mild elaboration of conventional beliefs as held by a proportion of the population	Vague sense that something is different, or not quite right with the world, a sense that things have changed but not able to be clearly articulated. Subject not concerned/ worried about this experience.	A feeling of perplexity. A stronger sense of uncertainty regarding thoughts than 2.	Referential ideas that certain events, objects or people have a particular and unusual significance. Feeling that experience may be coming from outside the self. Belief not held with conviction, subject able to question. Does not result in change in behaviour.	Unusual thoughts that contain completely original and highly improbable material. Subject can doubt (not held with delusional conviction), or which the subject does not believe all the time. May result in some change in behaviour, but minor.	Unusual thoughts containing original and highly improbable material held with delusional conviction (no doubt). May have marked impact on behaviour.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

Level of Distress (In Relation to Symptoms)

0 **100**
Not At All Distressed Extremely Distressed

1.2 NON-BIZARRE IDEAS

Non-Bizarre Ideas ('Crystallized Ideas')

- Suspiciousness, Persecutory Ideas: Has anybody been giving you a hard time or trying to hurt you? Do you feel like people have been talking about you, laughing at you, or watching you? What is it like? How do you know this?
- Grandiose Ideas: Have you been feeling that you are especially important in some way, or that you have powers to do things that other people can't do?
- Somatic Ideas: Have you had the feeling that something odd is going on with your body that you can't explain? What is it like? Do you feel that your body has changed in some way, or that there is a problem with your body shape?
- Ideas of Guilt: Do you feel you deserve punishment for anything you have done wrong?
- Nihilistic Ideas: Have you ever felt that you, or a part of you, did not exist, or was dead? Do you ever feel that the world does not exist?
- Jealous Ideas: Are you a jealous person? Do you worry about relationships that your spouse/girlfriend/boyfriend has with other people?
- Religious Ideas: Are you very religious? Have you had any religious experiences?
- Erotomanic Ideas: Is anyone in love with you? Who? How do you know this? Do you return his/her feelings?

NON-BIZARRE IDEAS - ELOBAL RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Psychotic and Severe**
No non-bizarre ideas.	Subtle changes that could be reality based. Eg. Very self-conscious.	Increased self-consciousness. Eg. Feeling that others look at the subject, or talk about the subject. Or feeling of increased self-importance. Subject able to question.	Odd or unusual thoughts but whose content is not entirely implausible- may be some logical evidence. More evidence than rating of 4. Content of thoughts not original i.e. jealousy, mild paranoia.	Clearly idiosyncratic beliefs, which although 'possible' have arisen without logical evidence. Less evidence than rating of 3. Eg. Thoughts that others wish the subject harm, which can be easily dismissed. Thoughts of having special powers, which can be easily dismissed.	Unusual thoughts about which there is some doubt (not held with delusional conviction), or which the subject does not believe all the time. May result in some change in behaviour, but minor.	Unusual thoughts containing original and highly improbable material held with delusional conviction (no doubt). May have marked impact on behaviour.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use/stress noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

Level of Distress (In Relation to Symptoms)

0 **100**
Not At All Distressed Extremely Distressed

1.3 PERCEPTUAL ABNORMALITIES

Visual Changes

- Distortions, illusions: Is there a change in the way things look to you? Do things somehow look different, or abnormal? Are there alterations in colour, or brightness of objects (things seeming brighter, or duller in colour)? Are there alterations in the size and shape of objects? Do things seem to be moving?
- Hallucinations: Do you have visions, or see things that may not really be there? Do you ever see things that others can't, or don't seem to? What do you see? At the time that you see these things, how real do they seem? Do you realise they are not real at the time, or only later?

Auditory Changes

- Distortions, illusions: Is there any change in the way things sound to you? Do things somehow sound different, or abnormal? Does your hearing seem more acute, or have increased sensitivity? Does your hearing seem muted, or less acute?
- Hallucinations: Do you ever hear things that may not really be there? Do you ever hear things that other people seem not to (such as sounds or voices)? What do you hear? At the time you hear these things, how real do they seem? Do you realise they are not real at the time, or only later?

Olfactory Changes

- Distortions, illusions: Does your sense of smell seem to be different, such as more, or less intense, than usual?
- Hallucinations: Do you ever smell things that other people don't notice? At the time, do these smells seem real? Do you realise they are not real at the time, or only later?

Gustatory Changes

- Distortions, illusions: Does your sense of taste seem to be different, such as more, or less intense, than usual?
- Hallucinations: Do you ever get any odd tastes in your mouth? At the time that you taste these things, how real do they seem? Do you realise they are not real at the time, or only later?

Tactile Changes

- Distortions, illusions, hallucinations: Do you ever get strange feelings on, or just beneath, your skin? At the time that you feel these things, how real do they seem? Do you realise they are not real at the time, or only later?

Somatic Changes

NOTE: Probes also used to rate Impaired Bodily Sensation, p.26

- Distortions, illusions: Do you ever get strange feelings in your body (eg feel that parts of your body have changed in some way, or that things are working differently)? Do you feel/think that there is a problem with some part, or all of your body, i.e. that it looks different to others, or is different in some way? How real does this seem?
- Hallucinations: Have you noticed any change in your bodily sensations, such as increased, or reduced intensity? Or unusual bodily sensations such as pulling feelings, aches, burning, numbness, vibrations?

PERCEPTUAL ABNORMALITIES - NLOBAL RATING SCALE

0 Never, absent	1 Questionable	2 Mild	3 Moderate	4 Moderately severe	5 Psychotic but not severe	6 Psychotic and severe
No abnormal perceptual experience.		Heightened, or dulled perceptions, distortions, illusions (eg lights/ shadows). Not particularly distressing. Hypnogogic/ hypnopompic experiences	More puzzling experiences: more intense/vivid distortions/ illusions, indistinct murmuring, etc. Subject unsure of nature of experiences. Able to dismiss. Not distressing. Derealisation/ depersonalis"	Much clearer experiences than 3 such as name being called, hearing phone ringing etc, but may be fleeting/ transient. Able to give plausible explanation for experience. May be associated with mild distress.	True hallucinations i.e. hearing voices or conversation, feeling something touching body. Subject able to question experience with effort. May be frightening or associated with some distress.	True hallucinations which the subject believes are true at the time of, and after, experiencing them. May be very distressing

Onset date: _____ ***Offset date:*** _____

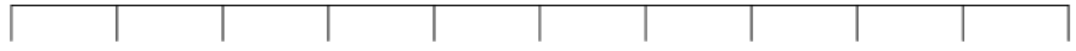
Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

Level of Distress (In Relation to Symptoms)



0 **100**
Not At All Distressed Extremely Distressed

1.4 DISORGANISED SPEECH

NOTE: Probes also used to rate Alogia, p. 16

Subjective Change:

- Do you notice any difficulties with your speech, or ability to communicate with others?
- Do you have trouble finding the correct word at the appropriate time?
- Do you ever use words that are not quite right, or totally irrelevant?
- Have you found yourself going off on tangents when speaking and never getting to the point? Is this a recent change?
- Are you aware that you are talking about irrelevant things, or going off the track?
- Do other people ever seem to have difficulty in understanding what you are trying to say/trouble getting your message across?
- Do you ever find yourself repeating the words of others?
- Do you ever have to use gesture or mime to communicate due to trouble getting your message across? How bad is this?
- Does it ever make you want to stay silent and not say anything?

Objective Rating of Disorganised Speech

- Is it difficult to follow what the subject is saying at times due to using incorrect words, being circumstantial or tangential?
- Is the subject vague, overly abstract or concrete? Can responses be condensed?
- Do they go off the subject often and get lost in their words? Do they appear to have difficulty finding the right words?
- Do they repeat words that you have used or adopt strange words (or 'non-words') in the course of regular conversation?

DISORGANISED SPEECH- ELOBAL RATING SCALE

0 Never, absent	1 Questionable	2 Mild	3 Moderate	4 Moderately severe	5 Severe	6 Psychotic
Normal logical speech, no disorganisation, no problems communicating or being understood.		Slight subjective difficulties eg problems getting message across. Not noticeable by others.	Somewhat vague, some evidence of circumstantiality, or irrelevance in speech. Feeling of not being understood.	Clear evidence of mild disconnected speech and thought patterns. Links between ideas rather tangential. Increased feeling of frustration in conversation.	Marked circumstantiality, or tangentiality in speech, but responds to structuring in interview. May have to resort to gesture, or mime to communicate.	Lack of coherence, unintelligible speech, significant difficulty following line of thought. Loose associations in speech.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

Level of Distress (In Relation to Symptoms)

0 **100**
Not At All Distressed Extremely Distressed

2: COGNITIVE CHANGE - ATTENTION/CONCENTRATION

2.1 SUBJECTIVE EXPERIENCE (HUBER'S BASIC SYMPTOM)

Concentration and Attention Problems:

- Have you had difficulty concentrating (difficulty listening to others, watching television, reading)?
- Is it more of an effort to think about, or concentrate on things?

Selective Attention Problems:

- Is it difficult to pay attention to just one thing?
- Are you distracted by other things easily?
- Have you been feeling overwhelmed, or confused by all the things that have been happening in the environment around you?

Thought Form Problems:

NOTE: See also Alogia, p. 16

- Do your thoughts ever seem to stop, get blocked, or disappear (e.g. do you have 'trances', or 'blank spells')? Can you describe this more fully?
- Do you ever experience racing or confused, jumbled thoughts?
- Do other things, as well as your thoughts, seem to stop e.g. attention, hearing, sight, memory, speech, or movement?
- Do you ever lose your sense of personal identity? What do you think was the cause of this?

Comprehension Difficulties:

- Do you have trouble following what others are saying?
- Do you sometimes require sentences to be repeated, especially long sentences?
- Do you sometimes not understand figures of speech and so on?
- Is this a change for you, or have you always had trouble with this?
- Do you ever have trouble picking up the emotional tone of conversations (eg. not recognising sarcasm, or irony)?
- Is it ever hard to understand non-verbal forms of communication i.e. gestures? How bad is this?

Memory Problems:

NOTE: See also Dissociative Symptoms, p.36

- Have you had memory problems?
- Have you ever felt as if there were large gaps in your memory?
- Are they present all the time, or do they come and go? Have you noticed if the memory problems come at times of stress?

SUBJECTIVE COGNITIVE CHANGE- AEVERITY RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No subjective difficulty with concentration /attention.	Subject aware of some changes, but attributable perhaps to extraneous factors. Subject has difficulty in pinpointing changes.	Mild, but definite problems eg some difficulty concentrating while reading, or watching TV. Concentrating requires more effort. **OR** Slight impairment in memory, but passing.	Subjectively feeling muddled, or confused, racing, or slowed thoughts, difficulty understanding conversations. Occ. episodes of thought blocking. **OR** Memory problems more evident but do not interfere with everyday functioning.	Subjective feeling of being unable to think properly, confused, unable to understand others. More regular episodes of thought blocking **OR** Memory difficulties impair conversation, results in frequent misplacing of items.	Marked inattentiveness, feeling confused and overwhelmed at times, distracted by other things in the environment. Frequent episodes of thought block. **OR** Memory difficulties noted by others, distressing.	Subject reports extreme difficulty focussing on interview. Interview suspended due to impossibility of patient to concentrate or severe thought blocking. **OR** Severe memory problems.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

2.2 OBSERVED COGNITIVE CHANGE

Observed Inattentiveness During Interview

- Subject appears inattentive - looks away during interview, does not pick up the topic during a discussion, shifts focus of attention.
- Attention may be drawn to noise in adjoining room, objects around the room, interviewer's clothing etc

Observed Inattentiveness During Mental Status Testing

- The subject may perform poorly on simple tests of intellectual functioning in spite of adequate education and intellectual ability.
- This is assessed by having the subject spell the word 'world' backwards and by serial 7s or serial 3s for a series of 5 subtractions.
- **D L R O W**
- **100, 93, 86, 79, 72**
- **100, 97, 94, 91, 88**

OBSERVED COGNITIVE CHANGE – AEVERITY RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No abnormalities observed.	Some questionable inattentiveness - may be explained by other events.	Mild problems with concentration. Objectively may be observed to shift focus of attention from interview 1 to 3 times. Not quite understanding what others are saying or the emotional tone of the conversation.	Moderate concentration problems during interview. Mild disruption to flow of interview as a result.	Poor concentration and attention significantly affect ability to perform tasks. Distractibility clearly observed to interfere with flow of the interview. .	Severe concentration and attention difficulties Extremely difficult to conduct interview, or pursue a topic due to preoccupation with irrelevant stimuli or	Inability to concentrate at all. Impossible to conduct interview due to preoccupation with irrelevant stimuli.

3: EMOTIONAL DISTURBANCE

3.1 SUBJECTIVE EMOTIONAL DISTURBANCE (HUBER'S BASIC SYMPTOM)

Impaired Emotional Functioning:

NOTE: See also Anhedonia, p. 18; Depression, p.29

- Have you noticed any change in your feelings, or emotions e.g. feel like you have no feelings, feel your emotions are 'empty', or that your emotions are somehow not genuine?
- Has there been any change in the way you are using your emotions?
- Have you still been able to enjoy things, or experience pleasure?
- Do you find that even when something sad happens, you are no longer able to feel sadness? Or when something happy happens, you can no longer feel happy?

Change in Affect:

Facial expressions:
- Have you noticed any change in your facial expressions?
- Have people commented on your facial expression, saying it is blank, or hard to know what you are thinking?

Eye contact:
- Has there been a change in the way you interact with other people e.g. do you find it hard to look at people when you speak to them?
- Has anyone commented on this?

Speech:
- Have you noticed a change in the way you talk, such as your voice becoming monotonous?
- Have people told you that you have a monotonous way of talking?
- Do they seem to find you boring?

Inappropriate affect:
- Have you ever felt different on the inside from the way you look to others?
- Like your appearance was uncoordinated with your emotions? Would you smile, or laugh when talking about something that was sad, or not funny at all?

SUBJECTIVE EMOTIONAL DISTURBANCE - SEVERITY RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No subjective change in feelings, or emotions.		Subjectively sporadic, mild, but definite problems reported eg not able to enjoy things as much as previously. Some feeling of blunting of emotional responses. Affect is inappropriate, but not sustained.	Subjectively, more frequent, or continuous problems. Some feeling of blunting of emotional responses. More pervasive feeling of inappropriate affect, but subject able to control somewhat.	Subject describes more marked change in emotions eg not able to express, or experience feelings as before. Sense of distance when with others. Inappropriate affect more difficult to hide from others.	Subject describes feeling of having no feelings, or emotions feel empty, or not genuine. Unable to feel sad at all. Severe degree of distance from others. Inappropriate affect interferes with relationships.	Subject reports constant emotional blunting, OR Inappropriate affect.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

3.2 OBSERVED BLUNTED AFFECT

NOTE: Incorporate informant information as well as interviewer's impression

- Rate observed evidence of blunting of affect. For example, diminished facial expressions, reduced emotional tone in speech, reduced expressive movements and gestures.
- The rater may also feel a diminished ability to engage the subject.

OBSERVED BLUNTED AFFECT – FEVERITY RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe, not psychotic**	6 **Extreme/ psychotic**
No abnormalities observed by interviewer, or others.		Slight degree of constriction of affect may be observed.	Observable constriction of emotional field. Avoidance or failure to display feelings. Reduced emotional expressivity. Interviewer feels a sense of 'distance', or decreased rapport.	More marked degree of dullness or blockade. Definite decrease in sense of rapport observed by interviewer. May have been reported, or commented on by informants.	Minimal evidence of affective display	Gross blunting of affect. No spontaneous emotional expression observed during interview. Definitely reported by informants.

Onset date: _____ ***Offset date:*** _____
(Do not score if relying on interviewer's report only- -3 on database)

Frequency and Duration
(Do not score if relying on interviewer's report only- -3 on database)

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

3.3 OBSERVED INAPPROPRIATE AFFECT

NOTE: Incorporate informant information as well as interviewer's impression

- Also rate clear-cut inappropriate affect (affect clearly discordant from the content of speech, or ideation (e.g. giggling when speaking of something sad).

OBSERVED INAPPROPRIATE AFFECT- FEVERITY RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No abnormalities observed by interviewer, or others.		Mild inappropriate affect during interview, or reported occasionally by others. Subject appears able to control.	More pervasive inappropriate emotion displayed. Does not dominate interview. Subject appears able to control somewhat.	More often reported by others- distracting during interview.	Inappropriate affect reported frequently. Interferes with social relationships and flow of interview.	Inappropriate affect throughout interview. Severely impacts on ability to conduct interview. Reported by others as occurring most of the time.

Onset date: _____ ***Offset date:*** _____
(Do not score if relying on interviewer's report only- Enter-3 on database)

Frequency and Duration
(Do not score if relying on interviewer's report only- Enter -3 on database)

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

4: NEGATIVE SYMPTOMS

4.1 ALOGIA

NOTE: Refer also to Cognitive Change, p.9; Disorganised Speech, p. 7

- Have you noticed problems trying to form conversations - i.e. hard to find words, thought blocking?
- Are the subject's responses to questions vague, or convey little information? Does the subject take a long time to respond to questions, but when prompted, displays an awareness of the question?

ALOGIA - OEVERITY RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No observed, or reported changes in speech.	Subject unsure about recent changes. Changes may be attributable to external factors, but subject unsure.	Very mild changes in ability to speak spontaneously Subject reports feeling "blocked" in their thinking. Difficulty finding words for thoughts. Not reported by others.	Difficulty expressing self in words - finding words, or more regular instances of thought blocking Observable by others, but not constant difficulty. Subject responds to prompting.	More marked poverty of speech, or thought blocking Does not significantly interfere with school, or work functioning.	Unable to express oneself adequately, or severe thought blocking May experience infrequent periods of mutism as a result of word finding and expression difficulties.	Marked poverty of speech or thought blocking. Seriously hinders flow of interview. Subject may be mute at times. Interferes significantly with ability to perform in social, occupation and educational settings.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

4.2 AVOLITION/APATHY (HUBER'S BASIC SYMPTOM)

Subjective Experience:

- Have you felt lacking in energy- mental and physical? Are you tired, or lacking in motivation, or 'get up and go'? Lack of will power? Lack of physical strength?
- To what extent does this interfere with activities such as going to school/work and other everyday tasks? How are you spending your days?

Observed Avolition/Apathy:

NOTE: Refer also to Disorganising/Odd/Stigmatising Behaviours, p.21

- Has the subject indicated difficulty maintaining the level of his/her usual social, or occupational/educational commitments?
- Does the subject appear to be looking after him/herself adequately- cleanliness/hygiene/general self-care?

Avolition/Apathy - Severity Rating Scale

0 Never, absent	1 Questionable	2 Mild	3 Moderate	4 Mod. Severe	5 Severe	6 Extreme
No observed, or reported changes in energy.	Subject unsure about recent changes. Changes may be attributable to external factors, but unclear.	Feeling fatigued, things are an effort. May not initiate activities as much as previously. Still able to perform everyday tasks. Does not interfere with schoolwork, or work attendance.	Feeling of reduced energy, or will power. Decreased attendance at school/work, or not performing usual tasks to usual ability. Not everyday and not reported by others.	More marked reduction in energy/ motivation. Some interference with normal functioning eg tasks take longer to do, subject doesn't bother to do some things. May miss school, or work a few times a week or frequently run late. May be unable to attend to personal hygiene as usual,	Daily reduction in energy, drive, will power, physical strength, or motivation. Interferes with normal functioning eg missing school, or work most day. Spends significant portions of time lying around. Clear impact on personal hygiene	Extreme and continuous disability eg unable to perform normal tasks, confined to house, no will power, or volition. Unable to attend school/work at all due to motivation. Marked impact on personal hygiene

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

4.3 ANHEDONIA

NOTE: Refer also to Depression, p. 29

- Have you been able to enjoy social activities/work/study as much as usual? _____
- Have you noticed a decrease in your level of interest in things you usually enjoy? _____
- Has this interfered with your ability to perform activities, e.g. going to school/work/participating in events? _____

ANHEDONIA- HEVERITY RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No observed, or reported changes in affect, speech, activity level, or attentiveness.	Some mild decrease in interest in events, but may be attributable to external cause (i.e. dislikes topic at school).	Some mild decrease in interest or enjoyment of activities. Not interfering with ability to perform them.	Moderate reduction in interest or enjoyment of activities such as school/work. May affect school/work performance.	Some regular experience of pleasure or humour but decreased in extent and quality. May impact on work/school attendance. Others concerned by associated withdrawal and isolation.	Rarely gains sense of enjoyment/ interest from tasks. At times able to enjoy something, but short lived. Poor attendance at school/work. Very noticeable by others.	No enjoyment or interest at all in tasks. Marked lack of interest. Isolated and withdrawn.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

5: BEHAVIOURAL CHANGE

Consider informant information as well as subjective report

5.1 SOCIAL ISOLATION

- Have you stayed at home more often than usual recently? Has this been by choice?
- Have you felt uncomfortable around others recently?
- Have you wanted to be alone more than usual recently? Has there been a reason for this? Have others commented on this?
- Have you missed important social events/school/work due to this?

Questions for informants:

- Has the subject been staying at home, perhaps in their room alone, more often than in the past? If so, do you know the reason for this?
- Have they missed social events/work/school due to this?
- Do they appear to want to spend time alone at present (more so than usual)?

SOCIAL ISOLATION- OEVERITY RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No change in level of social activity.		Subject feels that she/he does not want to fulfill all social/role functions. Wanting to be alone, but able to motivate self.	Isolating self at times, but not marked. Able to fulfill main role functions involving interactions with others. May miss some social activities.	Intolerant of being around others for long periods of time. Social withdrawal commented n by others. May miss 2-3 days week of school/work because of wanting to be alone.	Missing more days than not of work/school, spending greater part of day alone.	Isolated from others for extended periods (i.e. days)

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

5.2 Impaired Role Function

NOTE: See also Depression, p. 29

- Have you been able to attend school/work as usual recently?
- Has your school/work performance dropped recently?
- Have you been less interested in your work/school recently? Have others commented on this? Is there a reason for this? (Phrase questions appropriately i.e. for job seekers etc)

Questions for Informants:

- Have you noticed a change in attendance at work/school recently?
- Does the subject appear as capable at achieving normal tasks as usual?

Impaired Role Function- Neverity Rating Scale

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No recent change in role function.		Subject reports mild impairment in performance of usual activities. Not noted by informants.	Usual tasks performed with less care than usual. Missing occasional day of work/school. Noted as mild by informants.	Around half of usual time spent on normal daily tasks. Decreased quality of task performance noted by others.	Marked impairment of role functioning. Spending about half of day in aimless activity.	Subject attempting no role function whatsoever

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

5.3 DISORGANISING/ODD/STIGMATISING BEHAVIOUR

NOTE: See also Avolition, p.17; OCD, p.34; Social Isolation, p. 19

- Has there been anything about your lifestyle recently that others might regard as unusual, or odd? (Attempt to sensitively assess peculiar behaviours such as hoarding, talking to self, odd movements etc.)
- Have you been able to look after yourself as well as usual (Bathing, eating etc)? Has this been reported by others?

Questions for Informants:

- Have you noticed the subject behaving in an odd manner recently?
- Have you felt there is something strange about their behaviour? Has this been commented on by others?
- Have you noticed that they are hoarding goods, talking to self, moving in a bizarre fashion etc?

DISORGANISED/ODD/STIGMATISING BEHAVIOUR- HEVERITY RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No change in behaviour noted by subject, informants, or in interview.		Some reduction in self care, social isolation, but not marked. Subject able to motivate self to rectify this change. Slightly odd behaviour that would not normally attract attention of others, or conducted in private.	May require pressure from others to maintain social/ occupational commitments, or self care. Able to be motivated. Occasional odd behaviour that is noticeable by others (ie. giggling to self).	Mildly eccentric behaviour - clearly noticeable by others (ie talking to self/hoarding Not constant.	Clearly bizarre behaviour that attracts attention of others. Sometimes resulting in intervention by others.	Very poor self-care. Eccentric behaviours dominate clinical picture. May result in intervention by others. Odd behaviours may have negative impact on physical health. Extreme social isolation.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

5.4 Aggression/Dangerous Behaviour

- Have you been feeling angry, or irritable recently? Has there been a reason for this? Have you felt more irritated than usual at small things? Have you been in more arguments with others than usual recently? Have you been taking more risks (i.e. when driving) recently than usual? Have others commented that your behaviour is becoming risky, or unsafe? Have you felt like striking out at people or objects recently (more so than usual)?
- Have you become so angry at someone that you have had thoughts of hurting them, or destroying their property? Have you acted on these thoughts?

Questions for Informants:

- Has the subject been acting in an aggressive or dangerous manner recently? Have there been any recent episodes of anger outbursts/physical confrontation? Is this how the subject normally behaves? Have others commented on a change in their level of anger, or irritability? Has the subject destroyed property lately (in association with anger)? Have you felt safe with the subject recently (i.e. when driving, at otherwise normal times)?

Aggression/Dangerous Behaviour- Heverity Rating Scale

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No aggressive, or dangerous behaviour reported by the subject or others.		Slight irritability but not associated with rise in aggressive behaviour. May be attributed to events by subject.	More marked increase in irritability/anger towards self/others. May be expressed verbally, or physically in restrained manner (i.e punching pillow etc). May be noted by subject only.	Marked increase in irritability towards others expressed in increased propensity to verbal confrontations with threat of physical aggression. Noted by others and subject.	Aggressive behaviour results in property damage, or harm to others. Subject reports some level of control over anger.	Dangerousness in conjunction with anger at very destructive level, resulting in some considerable physical damage to others, or property. Dominates clinical picture. May attract attention of police etc.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

6: MOTOR/PHYSICAL CHANGES

6.1 SUBJECTIVE COMPLAINTS OF IMPAIRED MOTOR FUNCTIONING
(HUBER'S BASIC SYMPTOM)

Disorganised Movement:

- Have you noticed any change in the way you are moving e.g. clumsiness, lack of coordination, trouble organising your activities, or movements, loss of spontaneous movements?
- Have you noticed if your ability to perform some movements is distracted by other things?
- Does it require more effort or energy to perform some movements?

Mannerisms, Posturing:

- Have you developed any new movements, or poses (e.g. developed a nervous habit, a characteristic way of doing something, mimicking others, assuming certain postures)? What is your explanation for this?

SUBJECTIVE MOTOR CHANGE- AEVERITY RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No abnormal movements, or somatic difficulties reported by subject.		Mild changes only. Feeling clumsier, more uncoordinated than usual, feeling slightly slowed down. Occasional grimace, or mildly unusual gait	Experien-ces noted in column 1, but the subject feels a more noticeable change. Reports control over	Changes such as loss of coordination. Movements distracted by other things. Different gait, new poses, tics or mannerisms Loss of some previous abilities.	Experiences noted in column 4, but more distressing. May include episodes of mutism, bizarre postures, copying others movements.	Clearly distorted, or idiosyncratic movements, which dominate the clinical picture. Gross mannerisms, bizarre postures. Mute, or almost mute, with only very occasional spontaneous movements.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

6.2 Informant Reported or Observed Changes In Motor Functioning

Disorganised Movement:

- Have you noticed any change in the way you are moving e.g. clumsiness, lack of coordination, trouble organising your activities, or movements, loss of spontaneous movements?
- Have you noticed if your ability to perform some movements is distracted by other things?
- Does it require more effort or energy to perform some movements?

Mannerisms, Posturing:

- Have you developed any new movements, or poses (e.g. developed a nervous habit, a characteristic way of doing something, mimicking others, assuming certain postures)? What is your explanation for this?

Observed Motor Change- Aeverity Rating Scale

0 Never, absent	1 Questionable	2 Mild	3 Moderate	4 Moderately severe	5 Severe	6 Extreme
No abnormal movements, or somatic difficulties observed or reported by others.		Others report mild changes such eg. more clumsy, uncoordinated than usual, occasional grimace, or mildly unusual gait.	Experiences noted in column 1, but more marked. Subject appears to have some control over them.	Others report that subject having difficulty performing usual tasks i.e. driving. Has also developed new movements i.e. gait, new stance/ mannerisms. Some mimicking may also be reported.	Episodes of mutism and bizarre posturing reported. Not sustained- subject able to stop with assistance and effort.	Clearly distorted, or idiosyncratic movements, which dominate the clinical picture. Gross mannerisms, bizarre postures. Mute, or almost mute, with only very occasional spontaneous movements.

6.3 Subjective Complaints Of Impaired Bodily Sensation
(Huber's Basic Symptom)

NOTE: Refer also to p. 5 Perceptual Abnormalities

- Subjects say that there is something wrong with their bodily sensations.
- This includes disagreeable, but qualitatively normal sensations e.g pulling sensations, aches, pains, itching, burning, numbness, or qualitatively abnormal, unusual, or bizarre sensations may be described such as 'rustling' sensations in the eyes, vibrations, crawling sensations
- Do you ever get strange feelings in your body (eg feel that parts of your body have changed in some way, or that things are working differently)?
- Do you feel/think that there is a problem with some part, or all of your body, i.e. that it looks different to others, or is different in some way? How real does this seem?

Impaired Bodily Sensation- Ieverity Rating Scale

0 **Absent**	1 **Questionable**	2 **Mild,**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
Subject reports no change noticed in bodily sensations.		Subject notices occasional slight differences in bodily sensations. Not constant, able to ignore.	More intense changes to bodily sensations reported. Less able to ignore.	Occasional bizarre bodily sensation. Subject unsure of experience.	Subject reports more unusual, or bizarre sensations. Very distracting,	Subject reports extremely bizarre and unusual bodily sensations. May be distressing.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

6.4 Subjective Complaints Of Impaired Autonomic Functioning
(Huber's Basic Symptom)

Subjects may complain of something wrong with one, or more of their autonomic systems such as:

- The feeling of the heart racing, or going too slow, breathing too fast, or too deeply,
- Nausea,
- Increased sensitivity to the weather,
- Having to urinate more often, constipation,
- Poor sleep etc.

Impaired Autonomic Functioning: Severity Rating Scale

0 **Absent**	1 **Questionable**	2 **Mild,**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
Nothing reported.		Subject reports occasional change to autonomic functioning – e.g. fleeting panic sensations. No real impact on usual activities.	More enduring changes perceived – e.g. poor sleep over a number of nights. Mild interference with usual activities.	Numerous changes may be experienced simultaneously. Moderate interference with usual activities	Changes in autonomic functioning are distressing. Results in more marked disruption to usual activities	Subject reports constant and intense changes to autonomic functions. Very distressing.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

7: General Psychopathology

7.1 Mania

NOTE: See also Dangerous Behaviour/Aggression, p. 22

- Would you describe your mood as 'high', or 'hyper' recently?
- Have you been feeling excessively cheerful and had more energy than usual? How long has this feeling lasted?
- Have you felt out of control at these times?
- Has this feeling been in response to a substance, or event that has occurred (i.e. finished exams, new boyfriend/girlfriend etc)?
- Have you been able to stay awake doing things for longer periods of time than usual?
- Have you been sleeping less than usual?
- Have you found yourself spending more money than usual, or acting in ways you would not normally (i.e. heightened sexual drive, reckless behaviour etc)?
- Have you found your self, or have others described you, talking more than usual and faster than usual?
- Have people commented on your mood, or energy, saying you seem more energetic than usual, or out of control?
- Have you been feeling more irritable than usual recently? Has there been a reason for this?
- Have you been feeling better about yourself recently?
- Have you felt that you are special in some way, or have special powers, or skills?

MANIA- NEVERITY RATING SCALE

0 Never, absent	1 Questionable	2 Mild	3 Moderate	4 Moderately severe	5 Severe	6 Extreme
No observed, or reported elevation in mood. No change in self - opinion/ energy.		Cheerful without much reason. Unaccountable feelings of well-being that persist or Mild lability in mood Evidence of over-confidence with no real reason –within normal limits **&/OR** Some mild irritability	Reports excessive feelings of well-being, or cheerfulness without underlying reason Inappropriate to circumstances sometimes. More marked level of excitement. More prominent feels of self-importance. Overvalued ideas not delusional **&/OR** Moderate irritability	More persistent feelings of optimism, happiness, or elevated mood. Mood able to be shifted only with difficulty. Subject aware of inappropriateness of feelings. Behaviour may reflect the heightened mood. Clear cut grandiosity/belief in special powers - not all the time. More marked irritability evident/reported by others.	Mood elevated and inappropriate most of the time. Some delusional beliefs about own powers/ abilities. Highly distractable/ loosening of associations. Interview difficult.	Subject reports feeling elated, euphoric, marked increase in energy, restlessness. Behaviour may be destructive-excessive spending of money/sexual activity etc. Delusional beliefs of grandiosity/ power. Easily distractable, interview very difficult. Subject obviously irritable.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

7.2 DEPRESSION

NOTE: Refer also to: Avolition, p.17; Anhedonia, p.18; Role Functioning, p.20; Suicidality, p.31

- How would you describe your mood recently?
- Have you been feeling sad, or low? How often have you felt this way?
- Out of 10, what would be your average mood? Your lowest mood?
- Have you been able to enjoy activities, or feel good about yourself at all?
- How have you been feeling about the future (assess helplessness/hopelessness)?
- Has your interest in activities/events been lower than usual?
- Have you been able to complete, or start tasks you have been set (assess motivation)?
- How has your sleep been recently (assess change in sleep pattern/insomnia)?
- What has your appetite been like recently? Have you lost any weight?
- Have any events occurred recently that might account for these feelings (death/relationship issues/job/school)?

DEPRESSION- PEVERITY RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No reported depressed mood. No physical signs of depression.		Some feelings of sadness. Does not dominate clinical picture. Able to distract self from depressive thoughts. Depressive themes not spontaneously volunteered.	Evidence of more sustained lowered mood. More difficult to shift mood. Lowered mood may be impacting on level of motivation, but not significantly interfering with role functioning. May be slightly tearful, or sad expression in interview.	Stronger observational evidence of lowered mood. Reduced ability to react to pleasurable events. More regular 'tearful episodes'.	Severe depression - mood not able to be shifted. No evidence of delusional component. Some suicidality, but not acted upon. Biological changes consistent with lowered mood evident (appetite/sleep disturbance). Very low energy.	Abject misery. Delusional component to mood – i.e. nihilistic. More marked feelings of suicidality and associated behaviour.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

7.3 Suicidality and Self Harm

- Have you had any thoughts recently about harming, or killing yourself? How often have you felt this way?
- Have you had any thoughts of what you would do to achieve this?
- Have you acted on those thoughts at all? What happened?

Suicidality- Ieverity Rating Scale

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
Not present.		Occasional thoughts of being tired of living. Occasional thought of self-harm. No suicidal thoughts, or plans.	Feeling of being better off dead. Suicidal thoughts, with only vague plan. Able to be distracted from thoughts with some effort. **OR** Minor actions of self-harm (slight scratches etc).	Thoughts of suicide more frequent with associated plan. May be more seriously considering attempt with specific plan. **OR** Impulsive attempts using non-lethal method, or with knowledge of potential for being found.	Clear expression of wanting to kill self. **OR** Potentially serious, or lethal attempt with knowledge of possible rescue.	Specific plan and attempt. **OR** Serious attempt that clearly could have been fatal.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

7.4 Mood Swings/Lability

- Have you experienced mood swings recently?
- Have you felt that your moods have been up and down for no apparent reason?
- Do you find yourself happy one moment, and sad the next (or irritable), with no explanation?
- How often does this happen?
- Has this occurred in response to drugs, or events that have happened? Have others commented on this?
- How often has this occurred?

Mood Swings- Ieverity Rating Scale

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No evidence, or reported mood swings.		Subject reports feeling mood changes more easily than usual. More marked changes in response to external events. Not noticed/report-ed by others.	Subject reports more extreme changes in mood. Feeling that mood is out of control some of the time.	More pervasive experience of mood swings. Noted by others. Distressing. Interferes with normal activities.	Mood swings experienced more days than not. Significant interference with normal activities.	Subject reports that mood changes constantly and completely out of control. Unable to maintain normal level of activity.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

7.5 ANXIETY

- Have you been feeling nervous, or anxious recently? Has there been a reason for this? How often have you felt this way?
- How long does this feeling remain for?
- Have you felt panicky lately?
- Have you had times when you have felt breathless, heart racing, sweaty palms, tingling fingers, for no apparent reason?
- Do you have a phobia/are you afraid of dogs, spiders, enclosed places, crowds etc?
- Have you felt nervous around others recently (differentiate social anxiety from suspiciousness)?

ANXIETY- XEVERITY RATING SCALE

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No evidence, or reporting of anxiety.		Minor worries. Able to distract self from these. **&/OR** Mild physical signs of anxiety.	Moderate concerns, but level of anxiety is within appropriate range for event **&/OR** Moderate physical symptoms of anxiety.	Level of anxiety interfering slightly with normal activities. Some preoccupation with trigger. **&/OR** More marked physical signs.	More marked preoccupation with fears, sense of dread. **&/OR** Intrusive, distressing physical symptoms of anxiety	Level of anxiety disabling, feeling of panic, terrified.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

7.6 OCD Symptoms

- Do you have distressing, or intrusive thoughts that go round and round in your head that you cannot stop?
- Do you have any repetitive behaviours that you feel compelled to perform?
- Do you have anything that you do to stop 'bad things' from occurring (rituals/superstitions etc)?
- Do you have to have things a certain way, or you feel extremely anxious?
- Do you repeatedly check things, like light switches/gas/electrical appliances are switched off/doors locked etc?

OCD Symptoms- Meverity Rating Scale

0 **Never, absent**	1 **Questionable**	2 **Mild**	3 **Moderate**	4 **Moderately severe**	5 **Severe**	6 **Extreme**
No obsessional thoughts, or ruminations. No compulsive behaviour.		Some reported ruminating or compulsions, but not interfering with normal activities. Not time consuming Able to be distracted.	Some compulsive behaviours in response to obsessional thinking, but subject able to control. **&/OR** Compulsions do not distract from other activities.	Obsessional thinking distracting. interferes with ability to perform normal work/study. **&/OR** Compulsions not restricted to home, or private environment	Obsessional thinking or compulsions markedly distressing. **&/OR** Compulsions almost constantly - noticed by others.	Obsessional thoughts have quasi-delusional quality. **&/OR** Compulsions interfere with other activities, or are threatening to physical health (ie, hoarding garbage, excessive cleansing of body).

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

7.7 Dissociative Symptoms

Depersonalisation:
Have you experienced yourself as being unreal, as if you were outside your own body?
Or that part of your body did not belong to you?

Derealisation:
NOTE: See also Nihilistic Ideas, p.3
Have you had the feeling that things around you were unreal?

Dissociative Memory Problems:
NOTE: See also Cognitive Change, p.9
Have you ever found yourself a long way from your usual range of travel without any memory of how you got there?
Were you under stress then?

Dissociative Symptoms- Meverity Rating Scale

0 Never, absent	1 Questionable	2 Mild	3 Moderate	4 Moderately severe	5 Severe	6 Extreme
No reported feelings of depersonalis-ation/ dissociation.		Mild feeling of depersonalis-ation/ derealisation. Not distressing, or distracting.	More marked dissociative experiences. Some concern expressed by subject about these, but not marked concern.	Dissociative experiences associated with heightened concern/ Distress about these experiences.	Distress as a result of dissociative experiences. Interferes somewhat with usual activities (i.e. has to leave work/school/ social situation).	Feelings of depersonalis-ation/derealisation extremely distressing. Feeling of extreme distance from others. Marked periods of time when subject not able to describe what they have been doing, where they have been etc.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

7.8 Impaired Tolerance To Normal Stress
(Huber's Basic Symptom)

- Have you noticed a change in the way you have been coping with everyday stress?
- Have you felt less able to cope with, or tolerate everyday stress than before?
- When subjected to everyday stressors have you found yourself becoming excitable, uneasy, tense, nervous or anxious?
- Have you found that ordinary stressors increase other difficulties you have been experiencing?

Impaired Tolerance to Stress- Reverity Rating Scale

0 Never, absent	1 Questionable	2 Mild	3 Moderate	4 Moderately severe	5 Severe	6 Extreme
No subjectively impaired tolerance to normal stress.		Mild, or rare feeling of not coping as well as before.	Feeling mildly stressed in response to situations which would normally be coped with easily. Mild anxiety with everyday stressors, but still able to cope with them.	More marked feeling of high anxiety, or tension with everyday stressors, but able to perform everyday tasks. Feeling unable to cope with more stressful situations. May feel anxious for no reason infrequently.	Feelings of high anxiety, or tension with everyday stressors. Sometimes anxious for no reason at all.	Extreme disability eg. even trivial events, or minor concerns result in feelings of being overwhelmed and panicked. Very anxious all of the time, even if there is no apparent reason. Unable to adapt to novel situations.

Onset date: _____ ***Offset date:*** _____

Frequency and Duration

0	1	2	3	4	5	6
Absent	Less than once a month	Once a month to twice a week – **less** than one hour per occasion	Once a month to twice a week – **more** than one hour per occasion **OR** 3 to 6 times a week - **less** than one hour per occasion	3 to 6 times a week - **more** than an hour per occasion **OR** daily – **less** than an hour per occ.	Daily – **more** than an hour per occ. **OR** several times a day	Continuous

Pattern of Symptoms

0	1	2
No relation to substance use noted	Occurs in relation to substance use and at other times as well	Noted only in relation to substance use

8: INCLUSION CRITERIA

INTAKE CRITERIA CHECKLIST

Group 1: Vulnerability Group

This criterion identifies young people at risk of psychosis due to the combination of a trait risk factor and a significant deterioration in mental state and/or functioning

	YES	NO
• **Family history of psychosis** in first degree relative **OR Schizotypal Personality Disorder** in identified patient	☐	☐
PLUS		
• **30% drop in SOFAS** score from premorbid level, sustained for a month, occurred within past 12 months **OR SOFAS score of 50 or less** for past 12 months or longer	☐	☐
CRITERION MET FOR GROUP 1 – Vulnerability Group	☐	☐

Group 2: Attenuated Psychosis Group

This criterion identifies young people at risk of psychosis due to a subthreshold psychotic syndrome. That is, they have symptoms which do not reach threshold levels for psychosis due to subthreshold intensity (the symptoms are not severe enough) or they have psychotic symptoms but at a subthreshold frequency (the symptoms do not occur often enough).

	YES	NO
2a) Subthreshold Intensity:		
• **Global Rating Scale Score of 3-5** on *Unusual Thought Content* subscale, **3-5** on *Non-Bizarre Ideas* subscale, **3-4** on *Perceptual Abnormalities* subscale **and/or 4-5** on *Disorganised Speech* subscales of the CAARMS	☐	☐
PLUS		
• **Frequency Scale Score of 3-6** on *Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities* **and/or** *Disorganised Speech* subscales of the CAARMS for **at least a week** • **OR Frequency Scale Score of 2** on *Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities* and *Disorganised Speech* subscales of the CAARMS **on more than two occasions (experienced a minimum of four times in total)**	☐	☐
2b) Subthreshold frequency:		
• **Global Rating Scale Score of 6** on *Unusual Thought Content*, **6** on Non-Bizarre Ideas, **5-6** on *Perceptual Abnormalities* **and/or 6** on *Disorganised Speech* subscales of the CAARMS		
PLUS		
• **Frequency Scale Score of 3** on *Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities* **and/or** *Disorganised Speech* subscales of the CAARMS	☐	☐
PLUS (for both categories)		
• **Symptoms present in past year**	☐	☐
PLUS (for both categories)		
• **30% drop in SOFAS** score from premorbid level, sustained for a month, occurred within past 12 months **OR SOFAS score of 50 or less** for past 12 months or longer	☐	☐
CRITERION MET FOR GROUP 2 – Attenuated Psychosis Group	☐	☐

Group 3: BLIPS Group

This criterion identifies young people at risk of psychosis due to a recent history of frank psychotic symptoms that resolved spontaneously (without antipsychotic medication) within one week.

	YES	NO
• **Global Rating Scale Score of 6** on *Unusual Thought Content* subscale, **6** on *Non-Bizarre Ideas*, **5 or 6** on *Perceptual Abnormalities* subscale **and/or 6** on *Disorganised Speech* subscales of the CAARMS	☐	☐
PLUS		
• **Frequency Scale Score of 4-6** on *Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities* **and/or** *Disorganised Speech* subscales	☐	☐
PLUS		
• **Each episode of symptoms is present for less than one week** and symptoms spontaneously remit on every occasion.	☐	☐
PLUS		
• **Symptoms occurred during last year**	☐	☐
PLUS		
• **30% drop in SOFAS** score from premorbid level, sustained for a month, occurred within past 12 months **OR SOFAS score of 50 or less** for past 12 months or longer	☐	☐
CRITERION MET FOR GROUP 3 – BLIPS Group	☐	☐

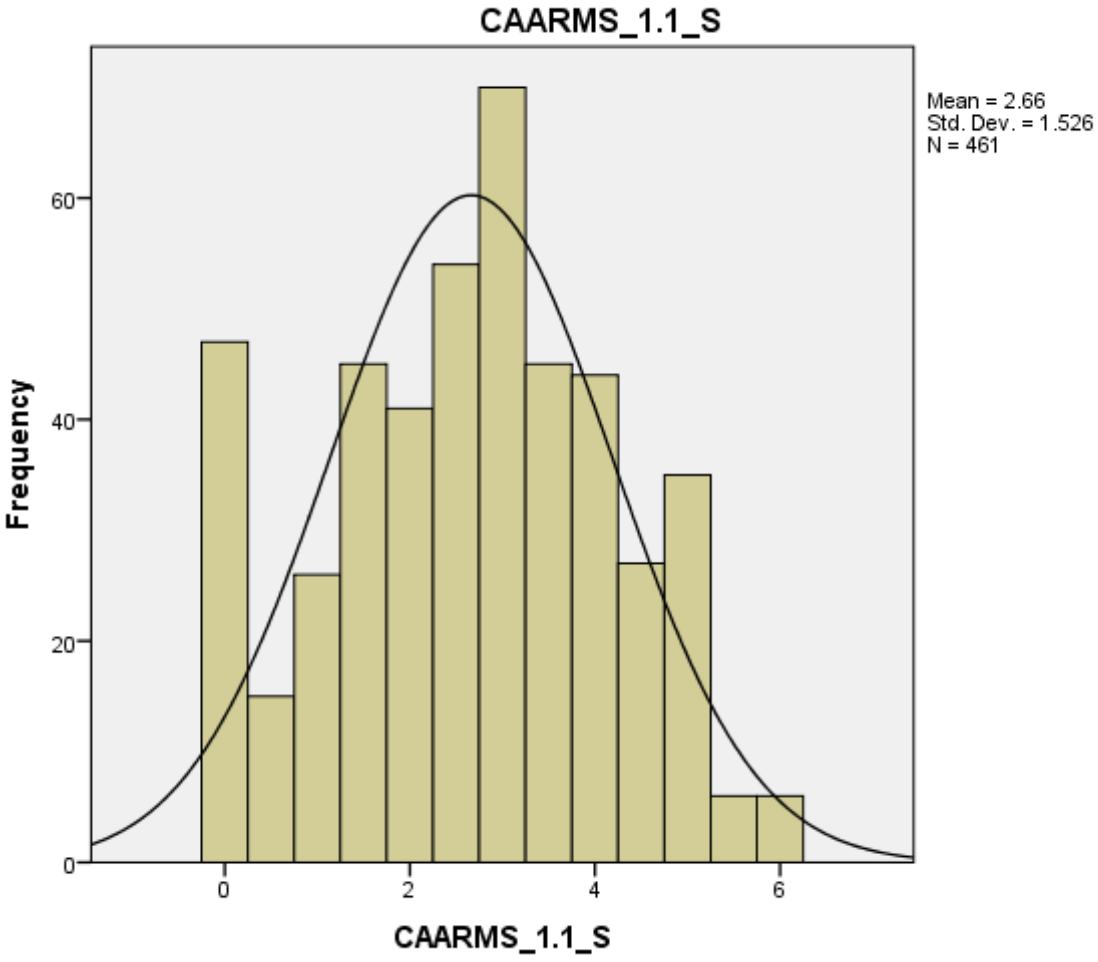
9: PSYCHOSIS THRESHOLD /ANTI-PSYCHOTIC TREATMENT THRESHOLD

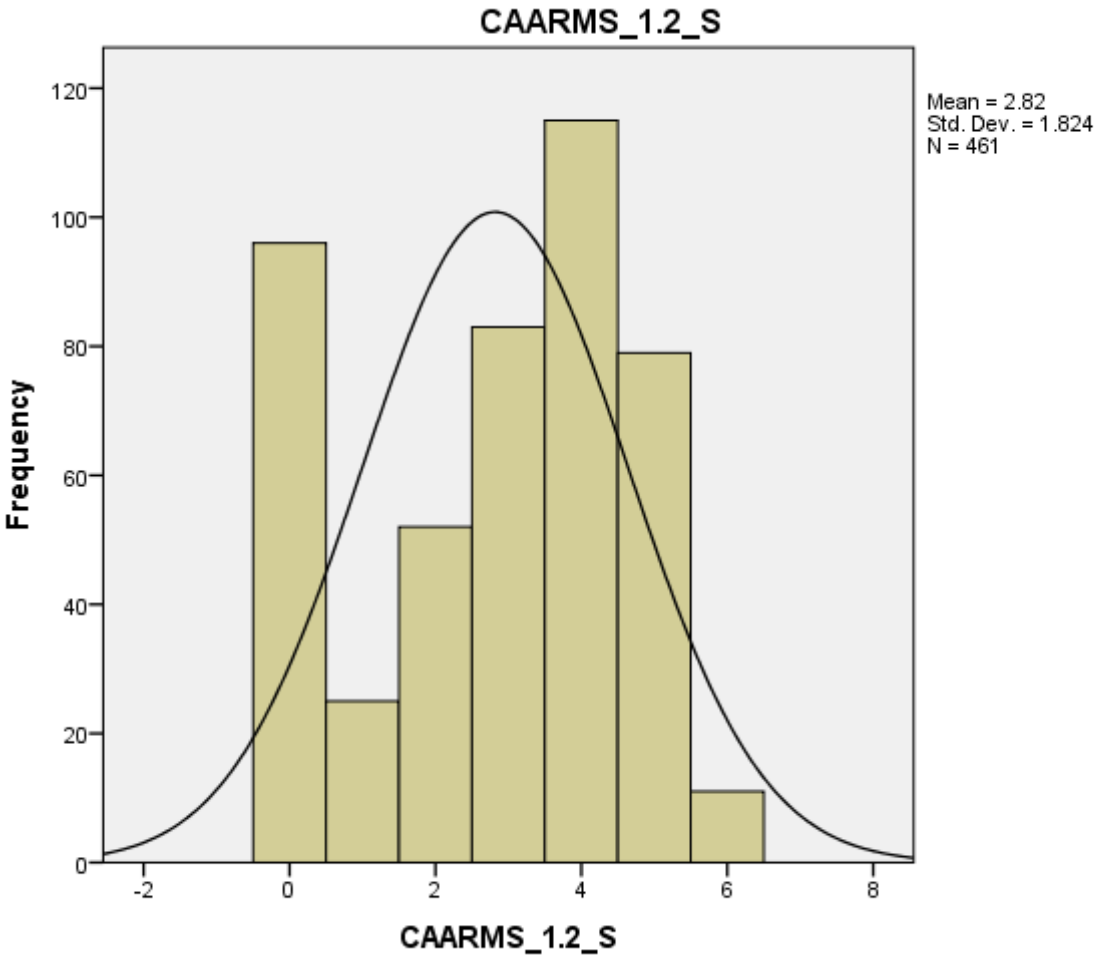
	YES	NO
• **Severity Scale Score of 6** on *Unusual Thought Content* subscale, **6** on *Non-Bizarre Ideas*, **5 or 6** on *Perceptual Abnormalities* subscale **and/or 6** on *Disorganised Speech* subscales of the CAARMS	☐	☐
PLUS		
• **Frequency Scale Score of greater than or equal to 4** on *Unusual Thought Content, Non-Bizarre Ideas, Perceptual Abnormalities* **and/or** *Disorganised Speech* subscales	☐	☐
PLUS		
• Symptoms present for **longer than one week**	☐	☐
PSYCHOSIS THRESHOLD CRITERION MET	☐	☐

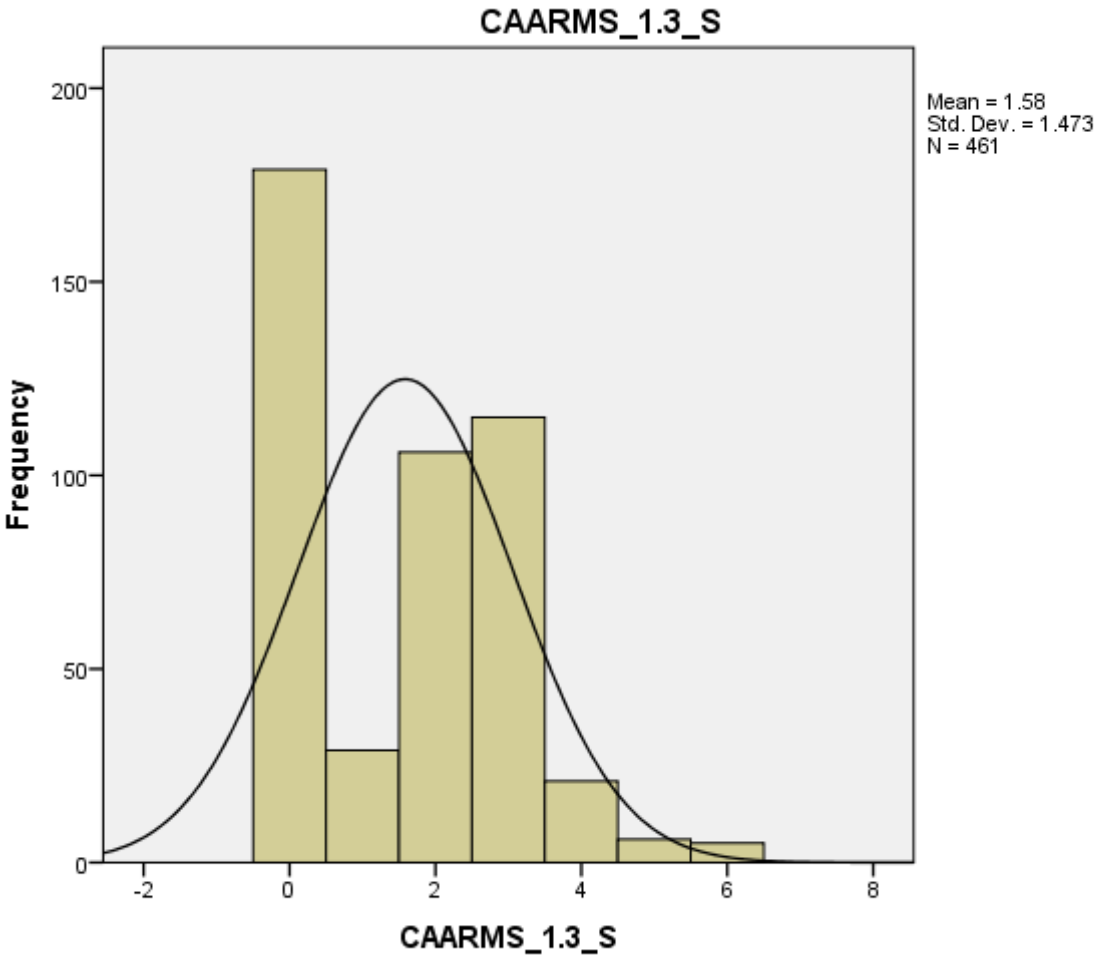
10: STUDY WITHDRAWAL ('BREAK BLIND') THRESHOLD

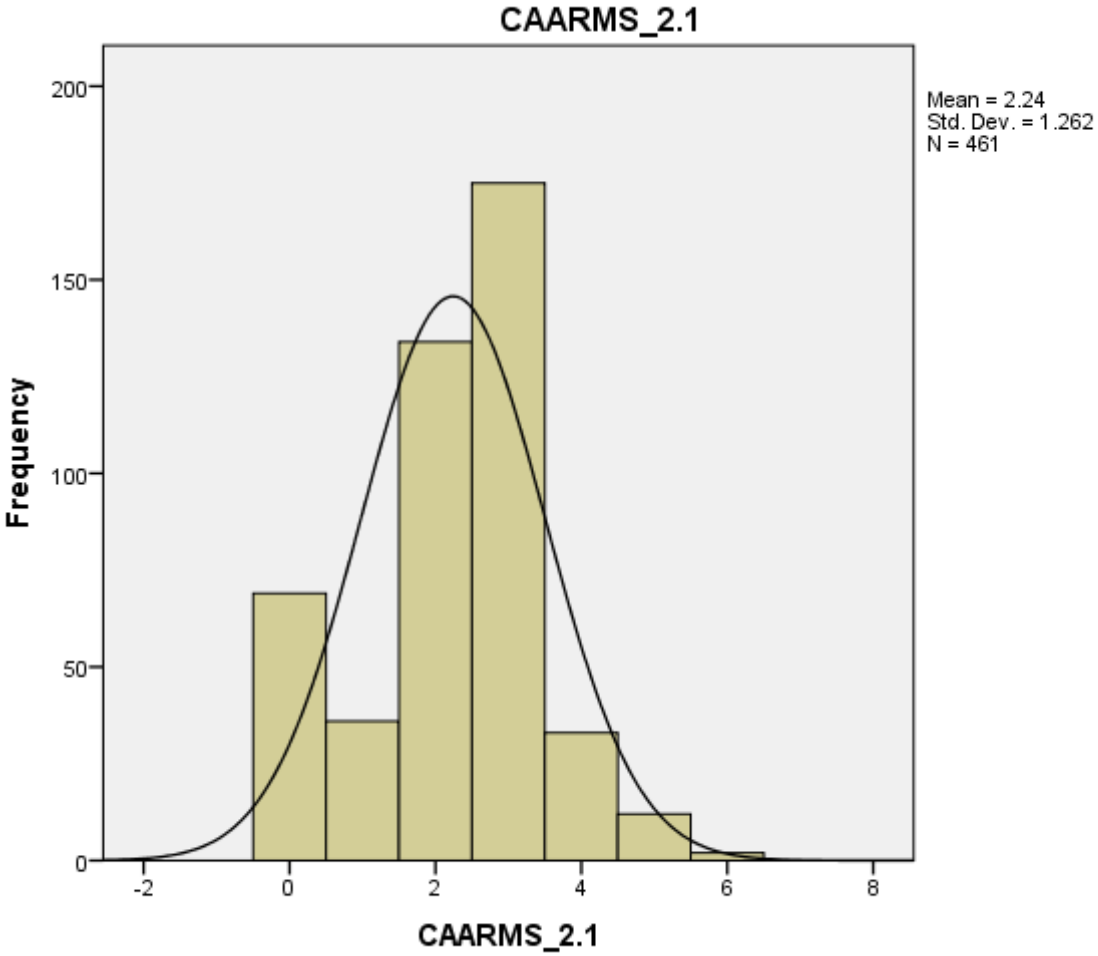
	YES	NO
• **Severity Scales Score of 5 or above** on *Aggression/Dangerous Behaviour* **and/or** *Suicidality/Self Harm* Subscales	☐	☐
• **NOTE:** This should be considered independently from level of psychosis		
STUDY WITHDRAWAL THRESHOLD CRITERION MET	☐	☐

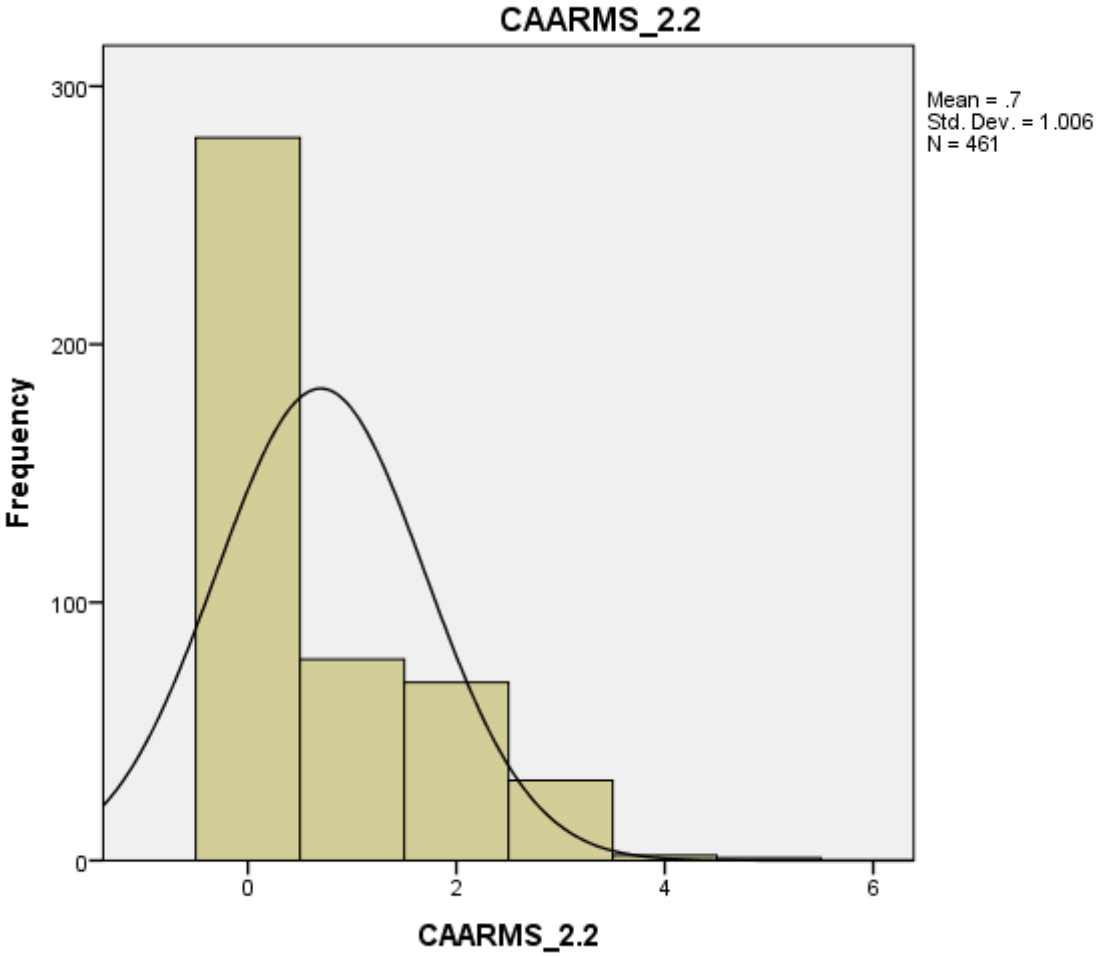
7.2 Appendix 2: Histograms of distribution of scores for 27 CAARMS Items

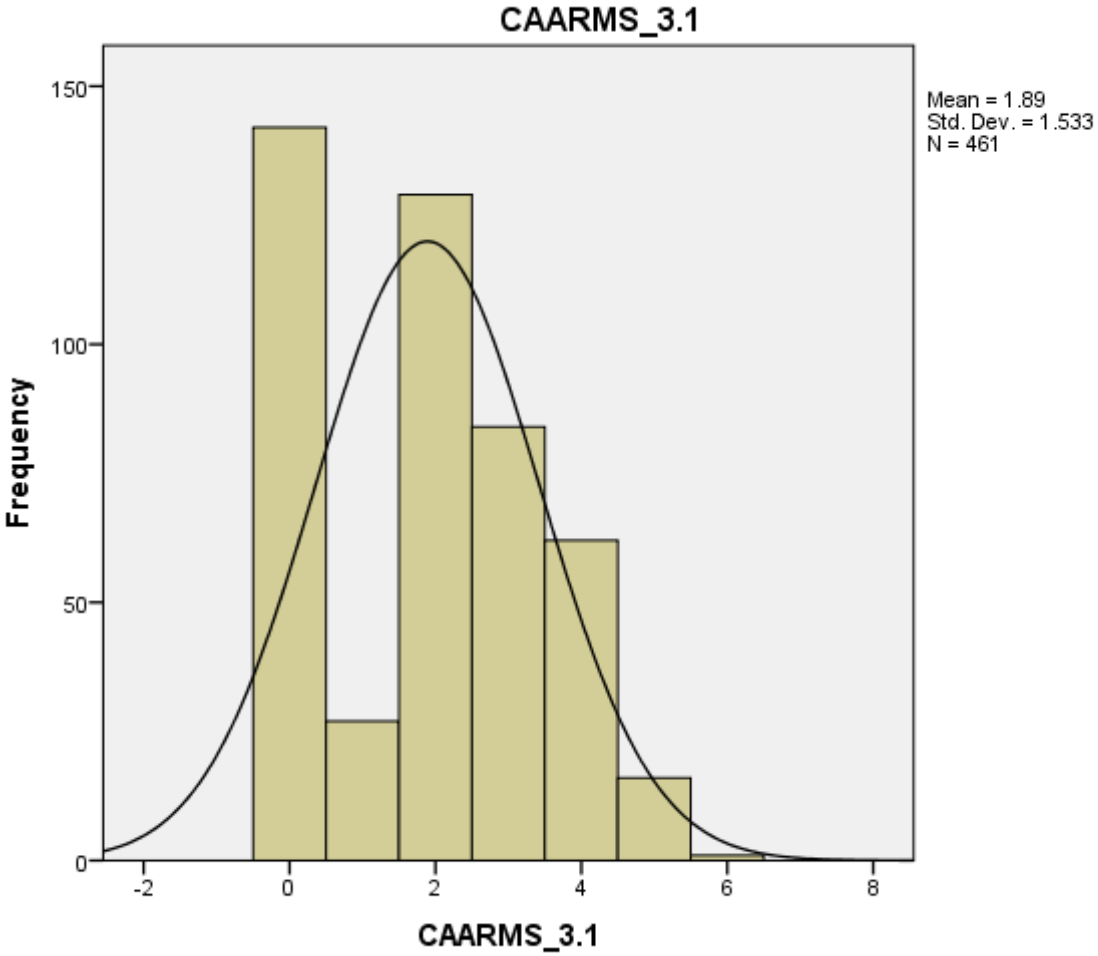


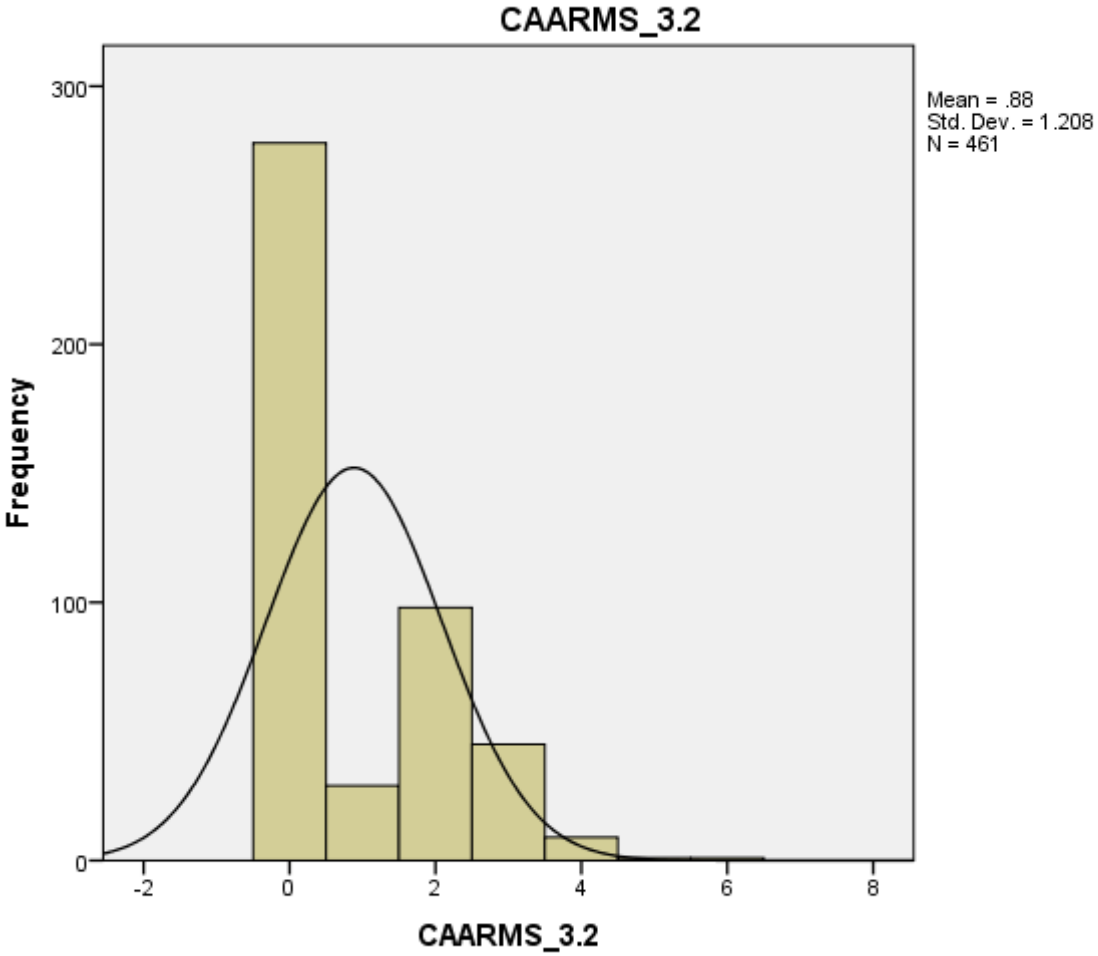

CAARMS_1.2_S
Mean = 2.82
Std. Dev. = 1.824
N = 461
Frequency
120
100
80
60
40
20
0
-2
0
2
4
6
8
CAARMS_1.2_S

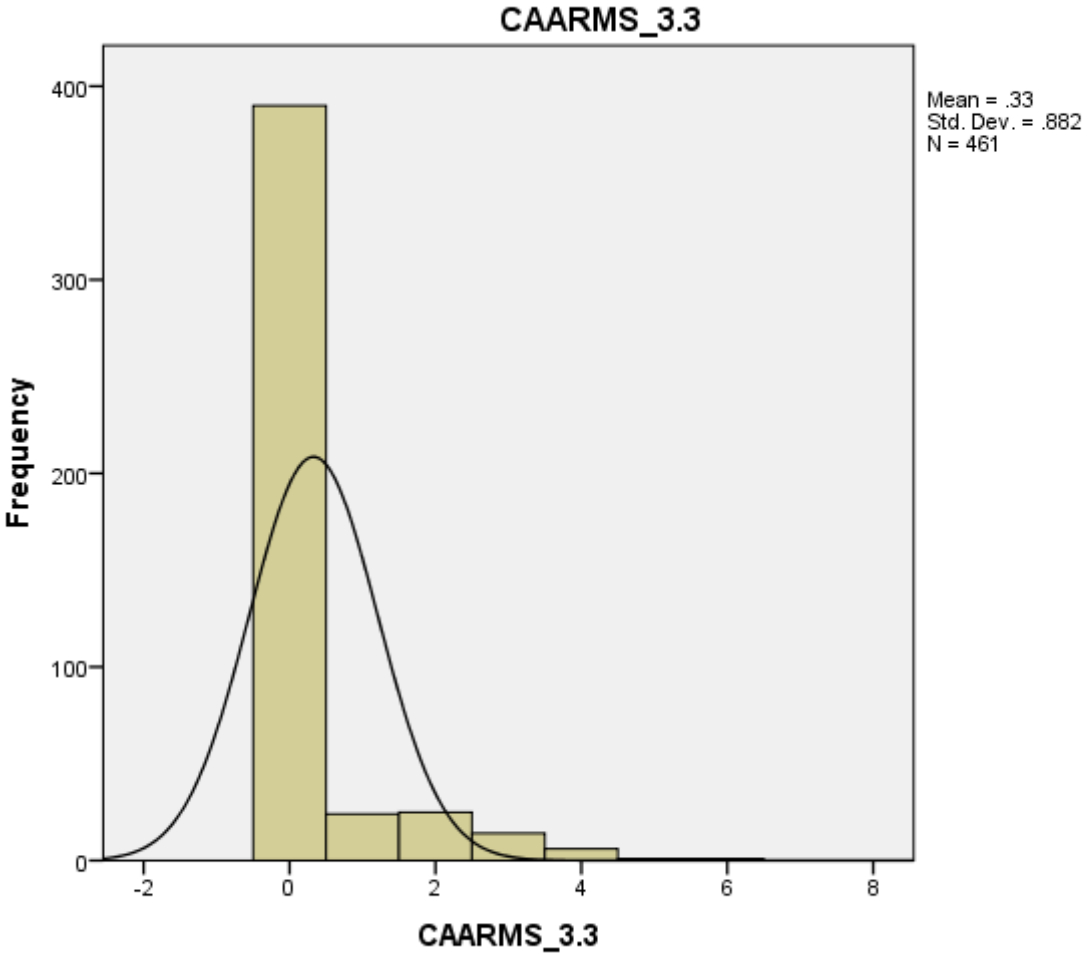

CAARMS_1.3_S
Mean = 1.58
Std. Dev. = 1.473
N = 461
Frequency
200
150
100
50
0
-2
0
2
4
6
8
CAARMS_1.3_S

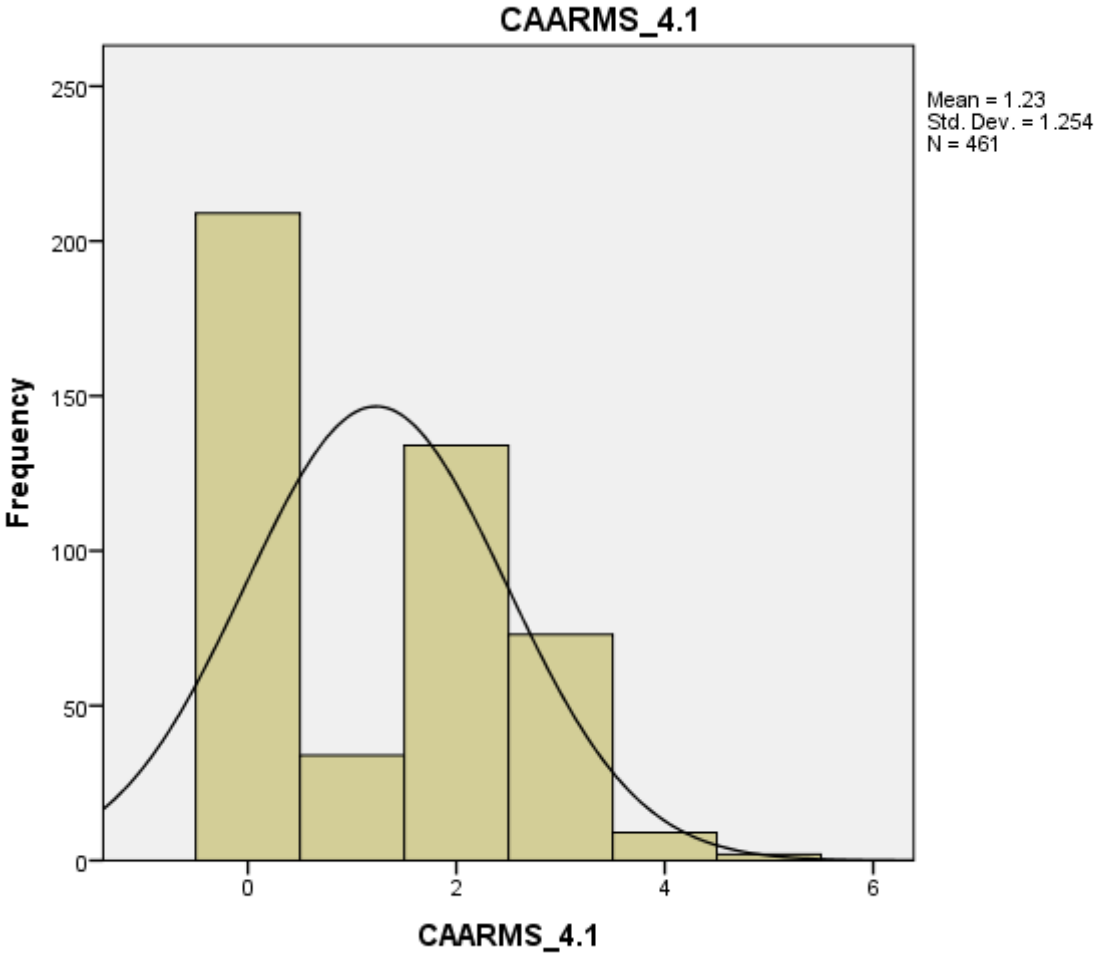

CAARMS_2.1
Mean = 2.24
Std. Dev. = 1.262
N = 461
Frequency
200
150
100
50
0
-2
0
2
4
6
8
CAARMS_2.1

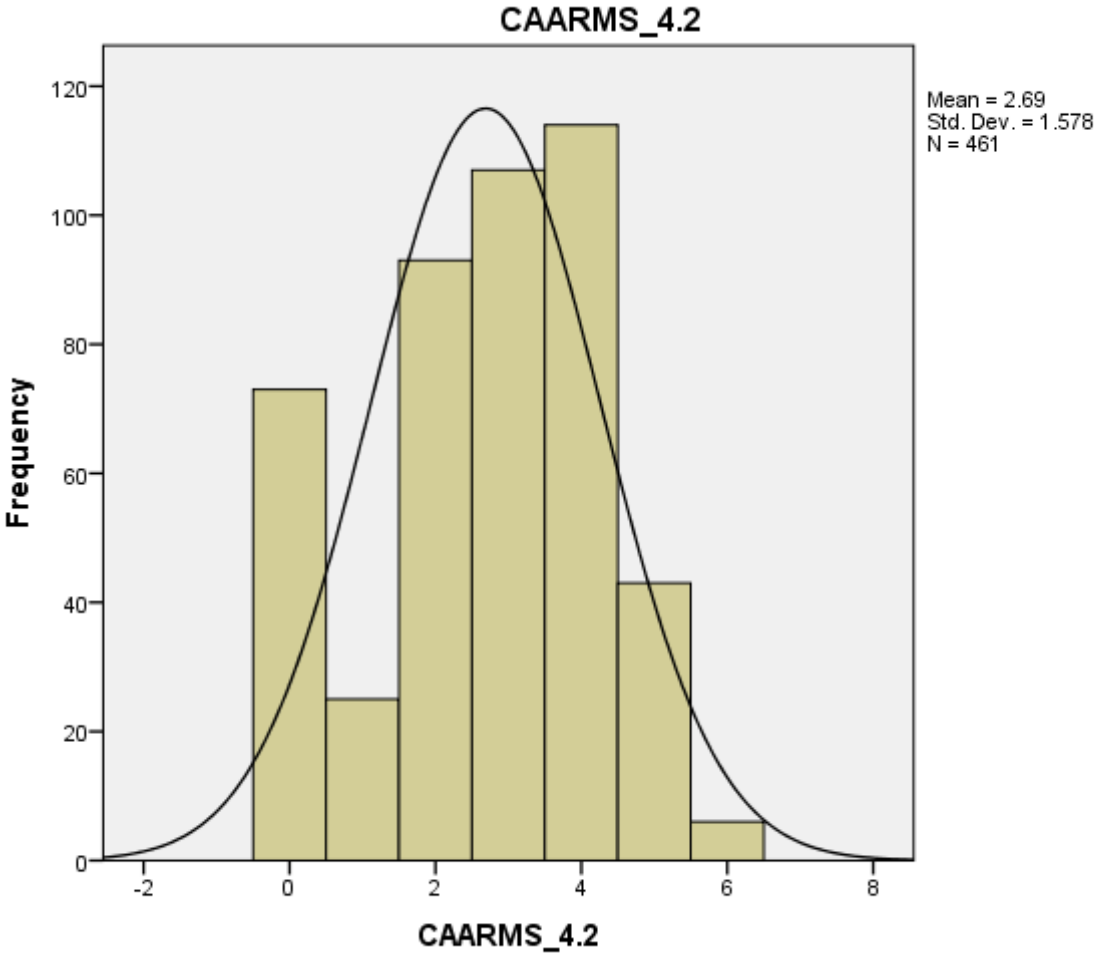

CAARMS_2.2
Mean = .7
Std. Dev. = 1.006
N = 461
Frequency
300
200
100
0
0
2
4
6
CAARMS_2.2

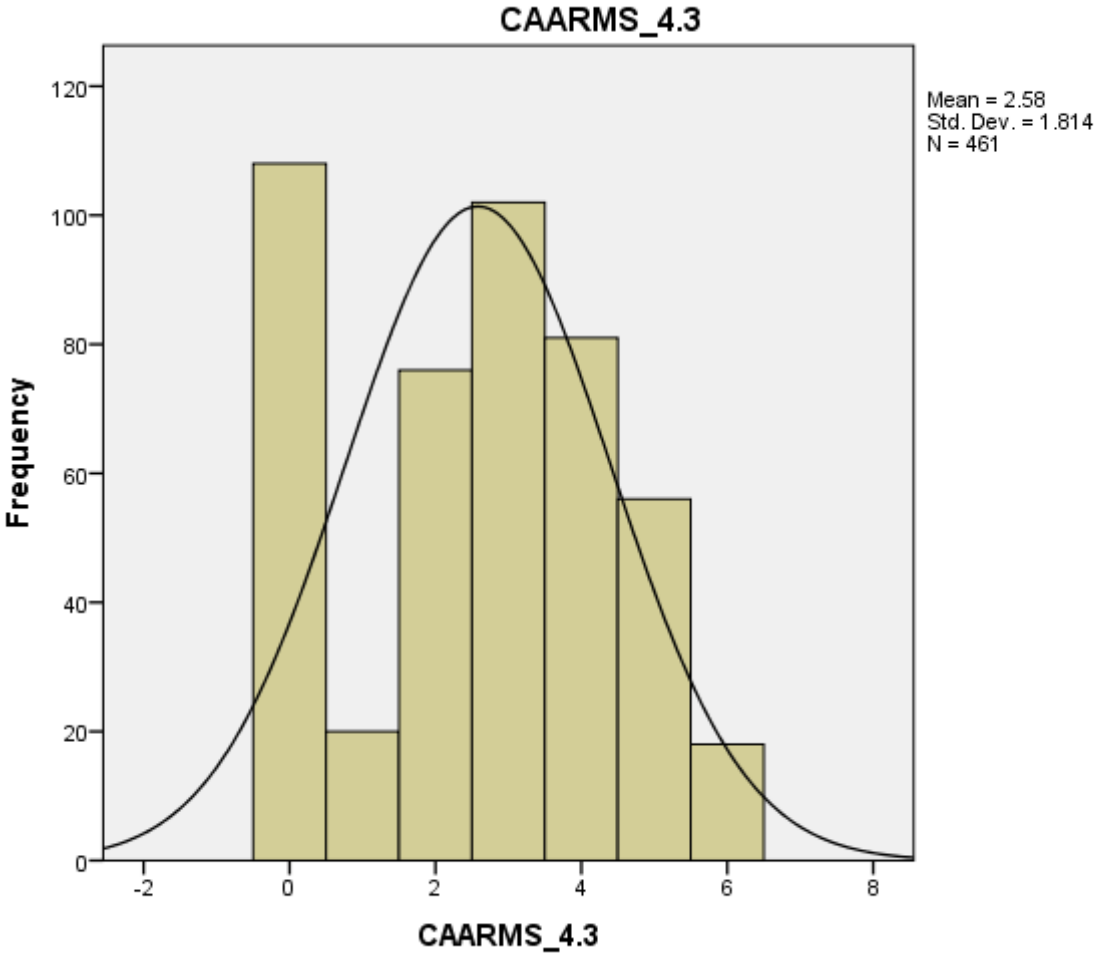

CAARMS_3.1
Mean = 1.89
Std. Dev. = 1.533
N = 461
Frequency
150
100
50
0
-2
0
2
4
6
8
CAARMS_3.1

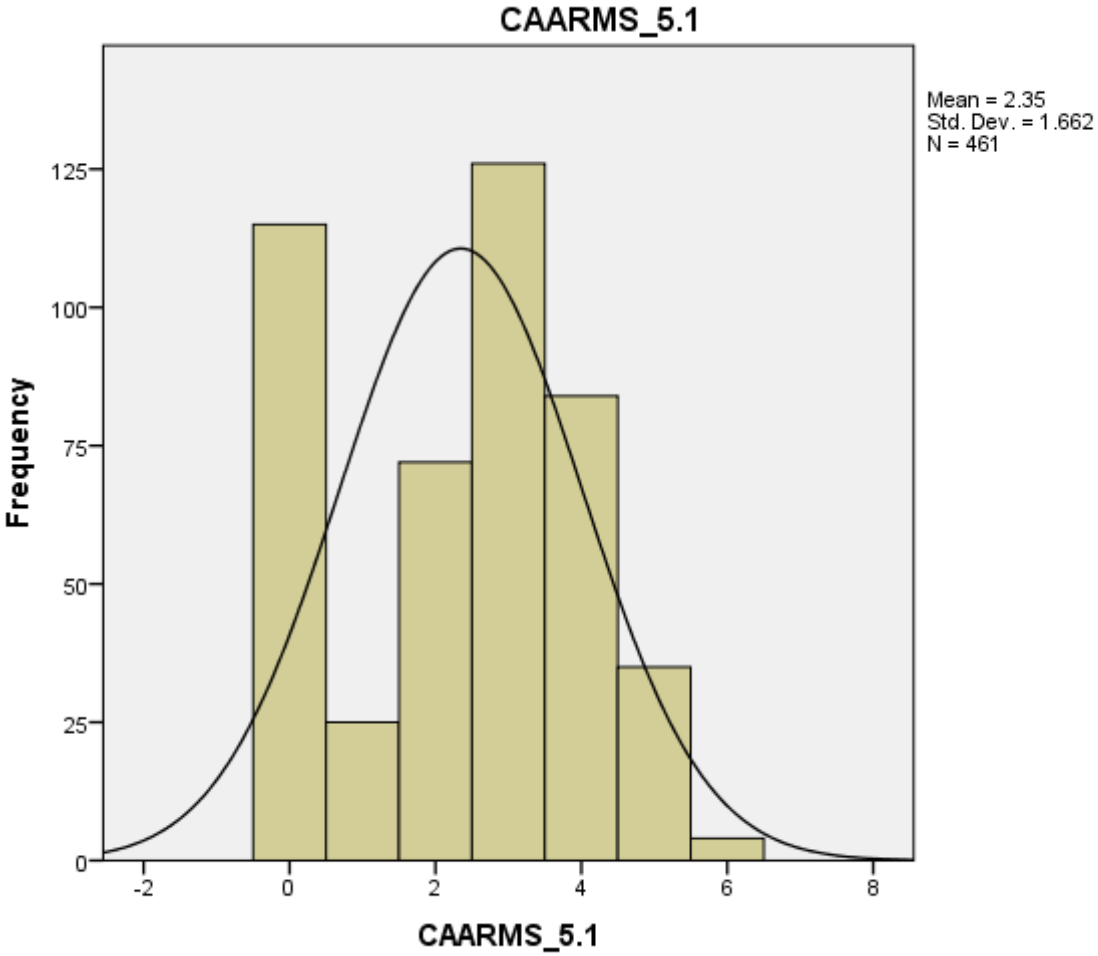

CAARMS_3.2
Mean = .88
Std. Dev. = 1.208
N = 461
Frequency
300
200
100
0
-2
0
2
4
6
8
CAARMS_3.2

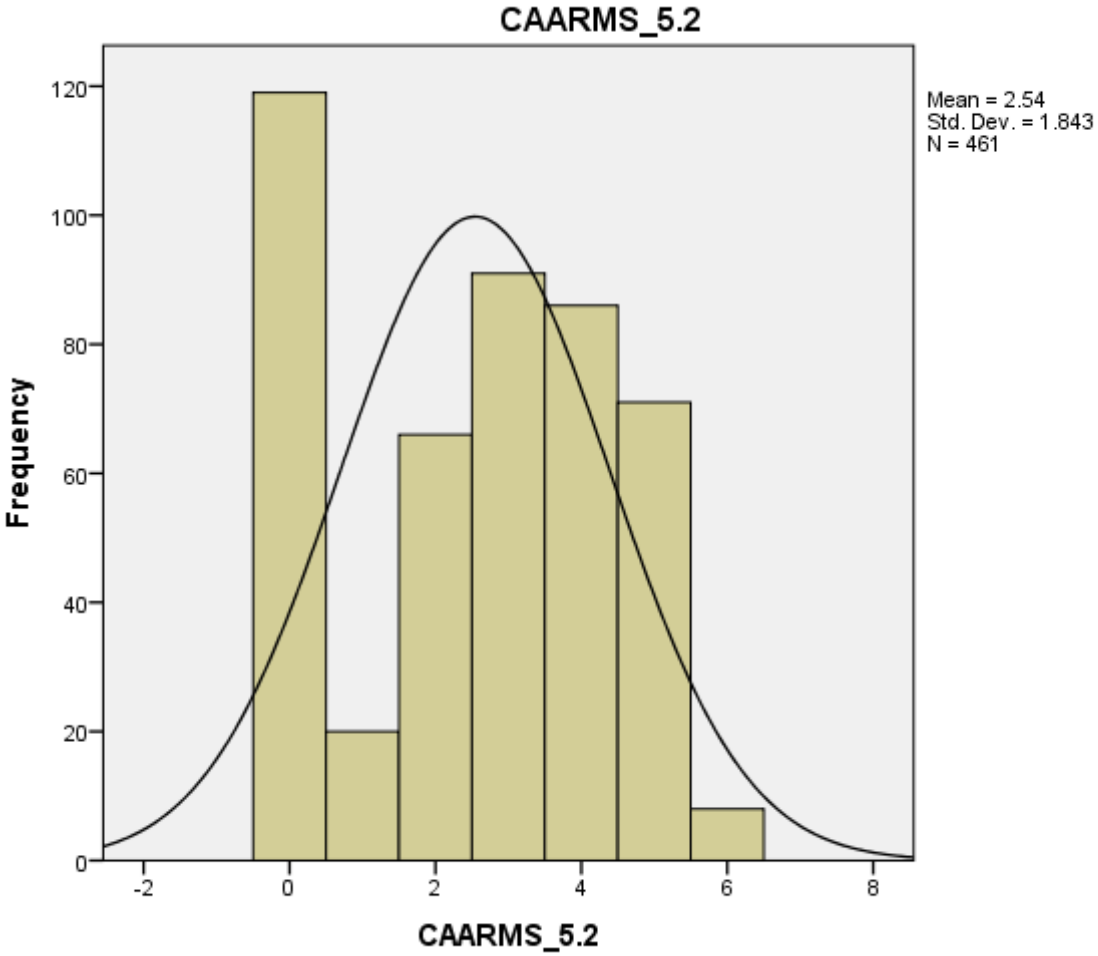

CAARMS_3.3
Mean = .33
Std. Dev. = .882
N = 461
Frequency
400
300
200
100
0
-2
0
2
4
6
8
CAARMS_3.3

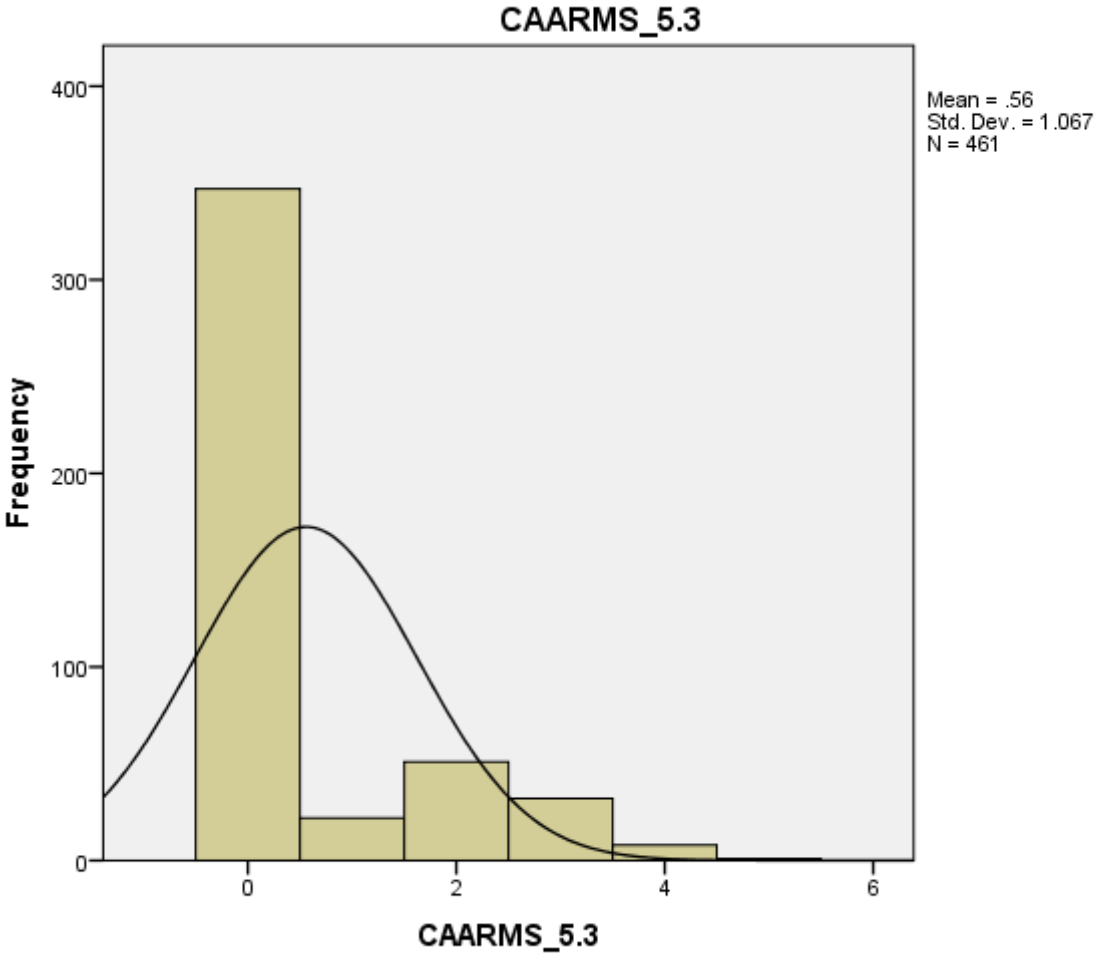

CAARMS_4.1
Mean = 1.23
Std. Dev. = 1.254
N = 461
Frequency
250
200
150
100
50
0
0
2
4
6
CAARMS_4.1

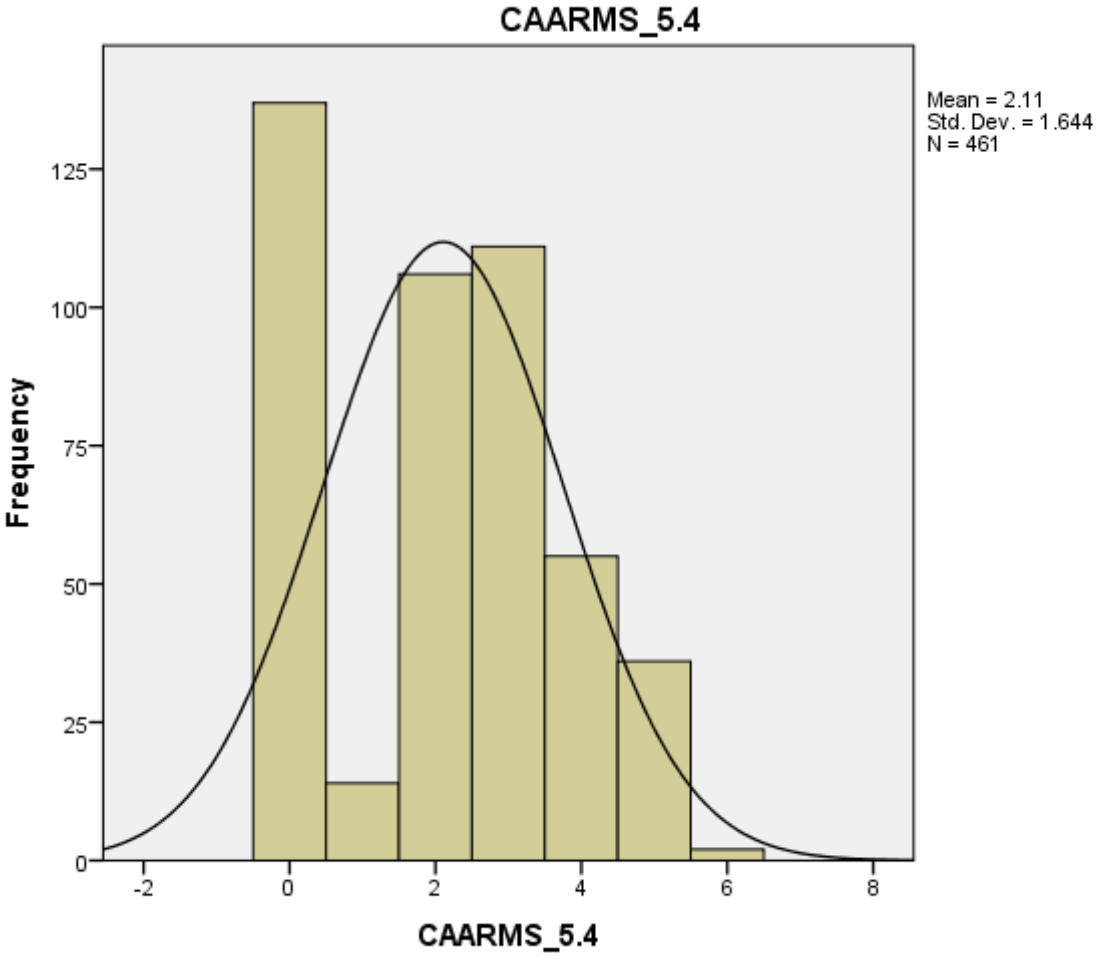

CAARMS_4.2
Mean = 2.69
Std. Dev. = 1.578
N = 461
Frequency
120
100
80
60
40
20
0
-2
0
2
4
6
8
CAARMS_4.2

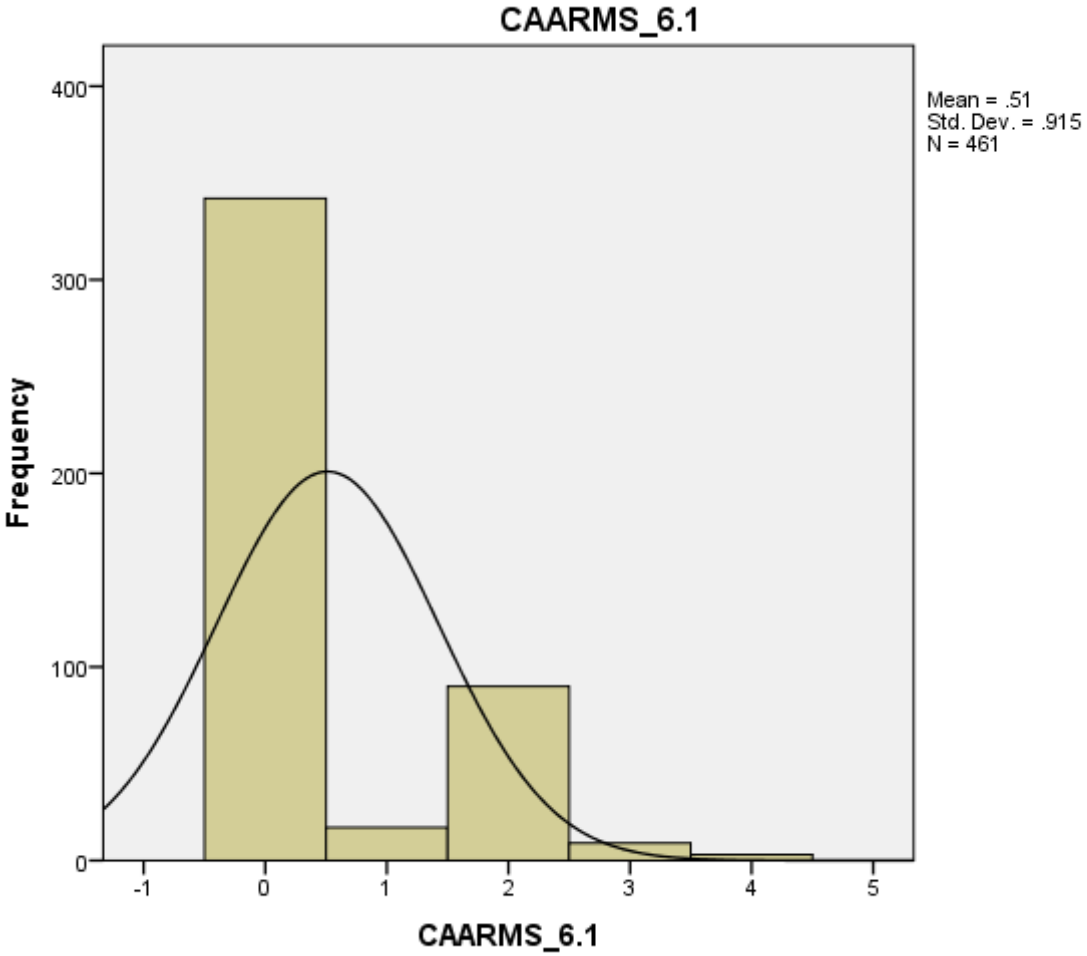

CAARMS_4.3
Mean = 2.58
Std. Dev. = 1.814
N = 461
Frequency
120
100
80
60
40
20
0
-2
0
2
4
6
8
CAARMS_4.3

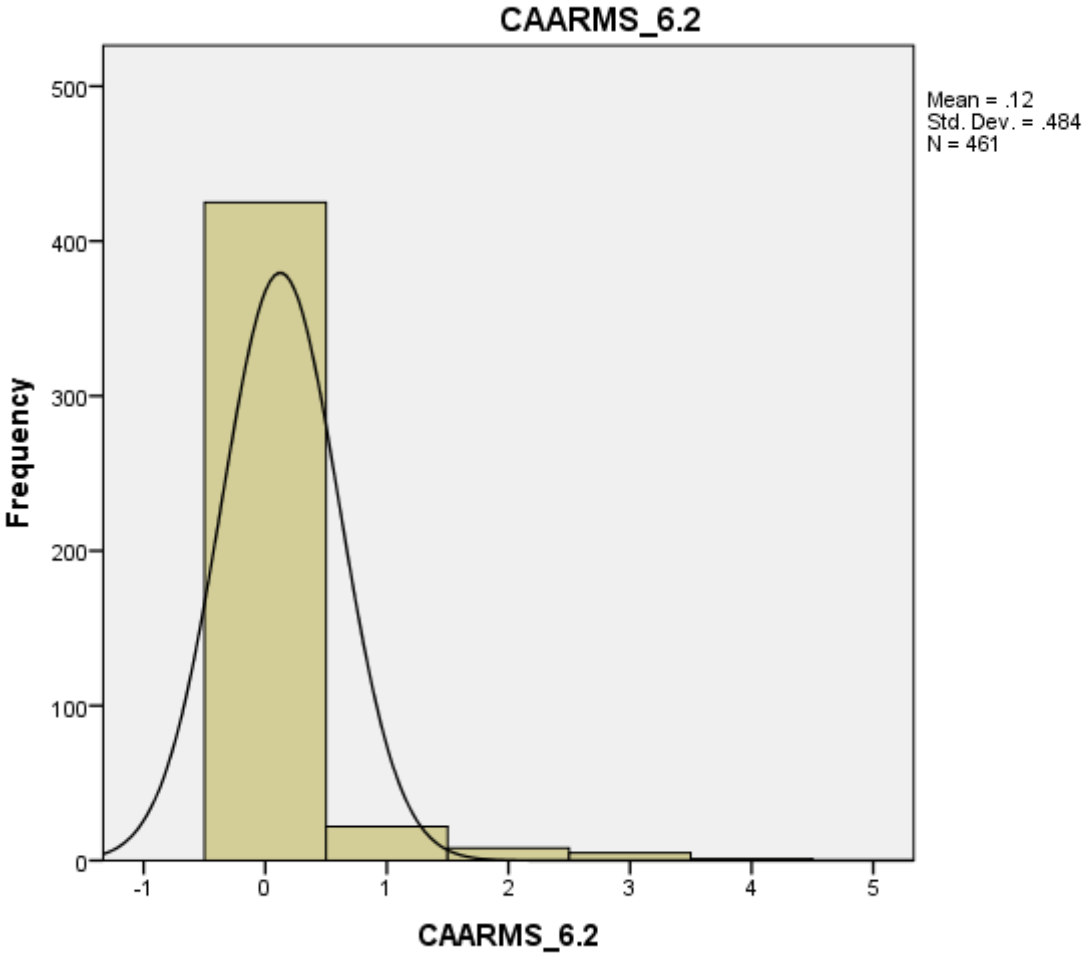

CAARMS_5.1
Mean = 2.35
Std. Dev. = 1.662
N = 461
Frequency
125
100
75
50
25
0
-2
0
2
4
6
8
CAARMS_5.1

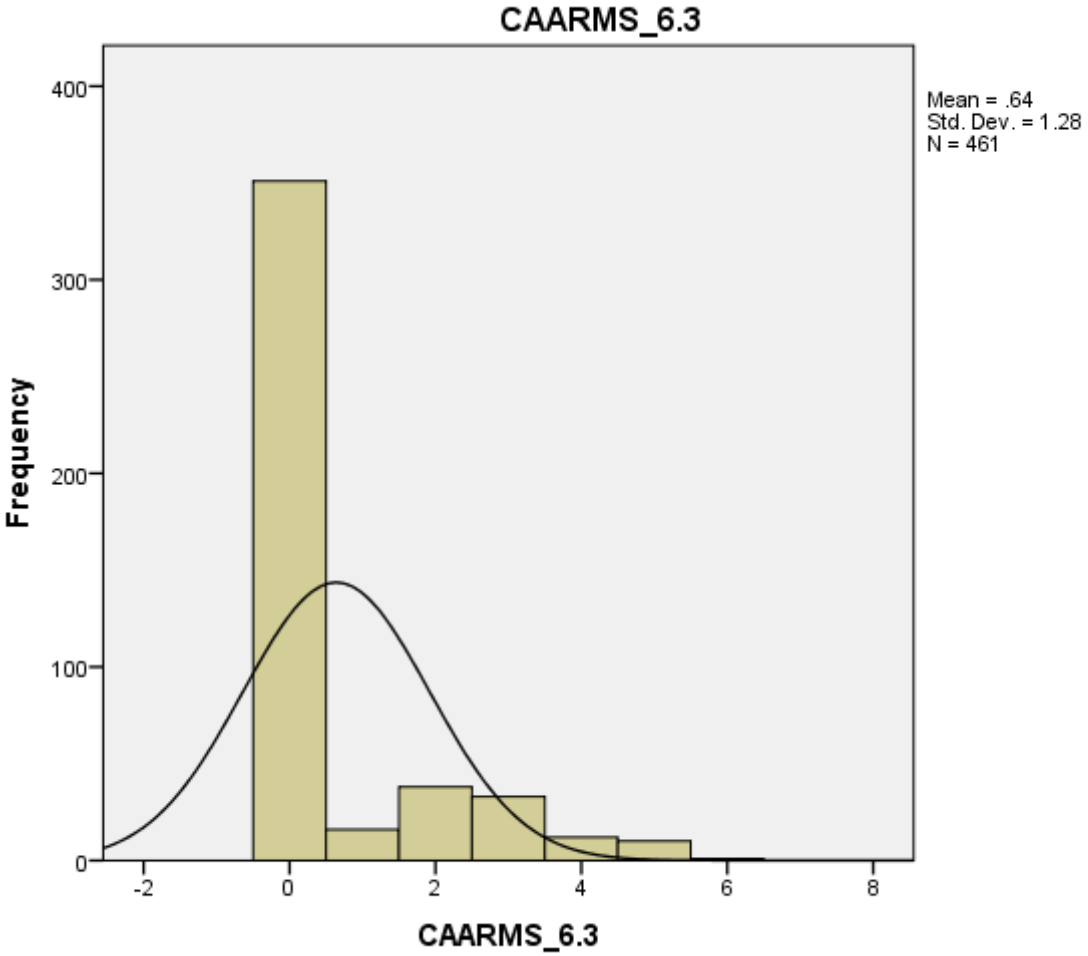

CAARMS_5.2
Mean = 2.54
Std. Dev. = 1.843
N = 461
Frequency
120
100
80
60
40
20
0
-2
0
2
4
6
8
CAARMS_5.2

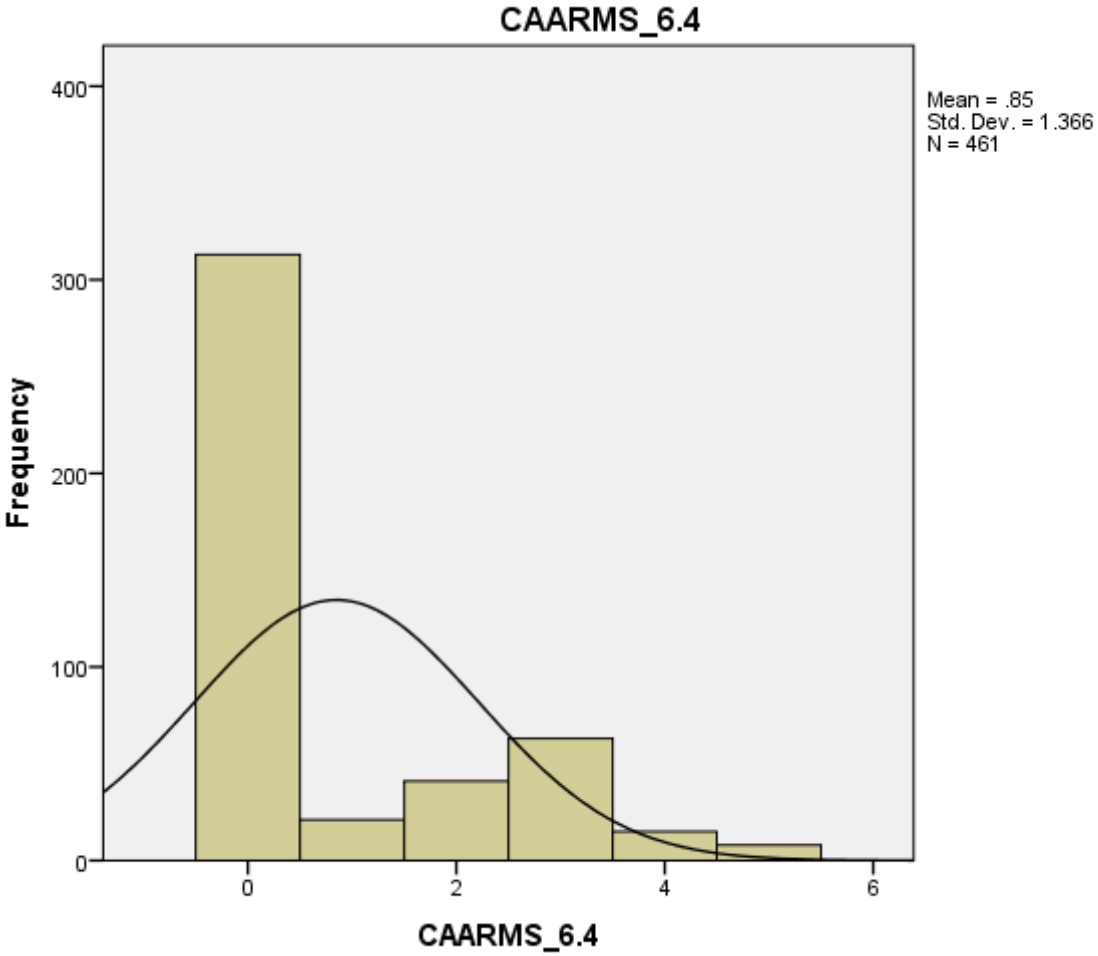

CAARMS_5.3
Mean = .56
Std. Dev. = 1.067
N = 461
Frequency
400
300
200
100
0
0
2
4
6
CAARMS_5.3

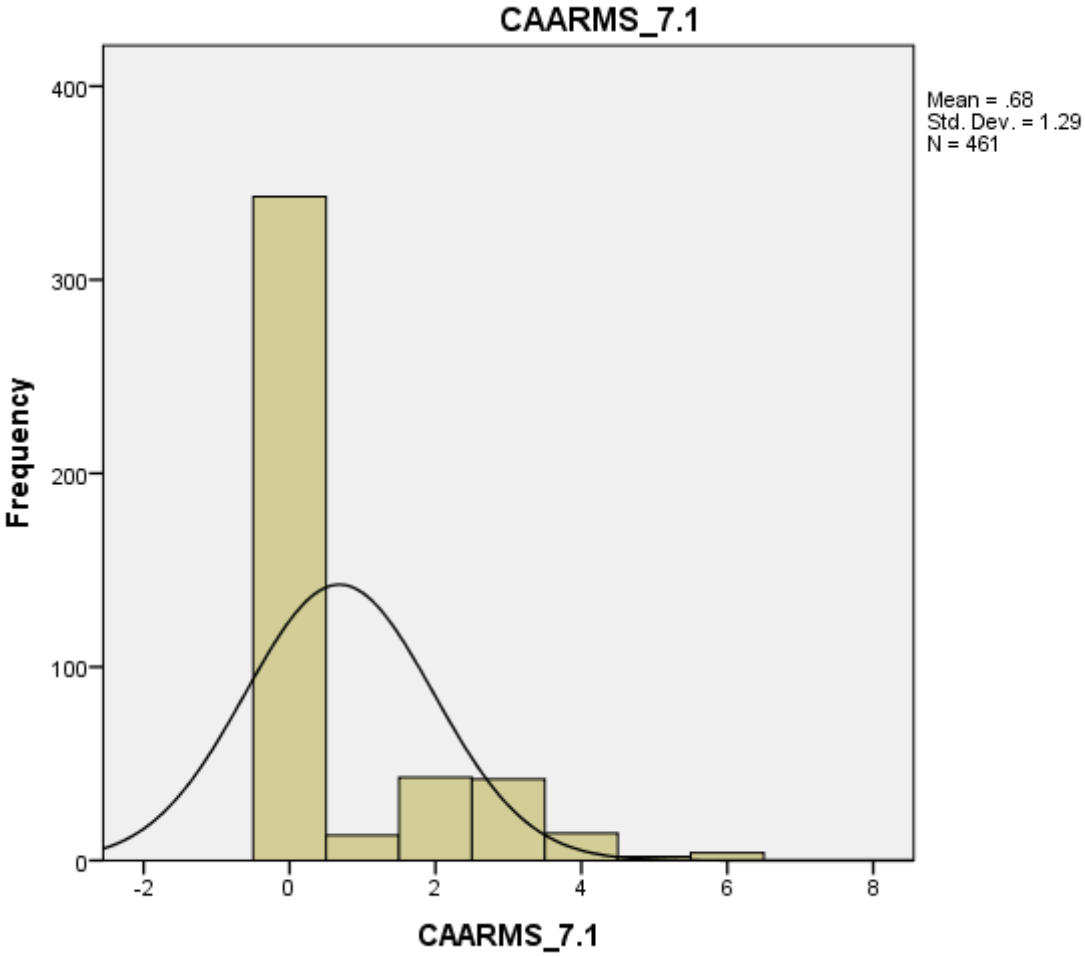

CAARMS_5.4
Mean = 2.11
Std. Dev. = 1.644
N = 461
Frequency
125
100
75
50
25
0
-2
0
2
4
6
8
CAARMS_5.4

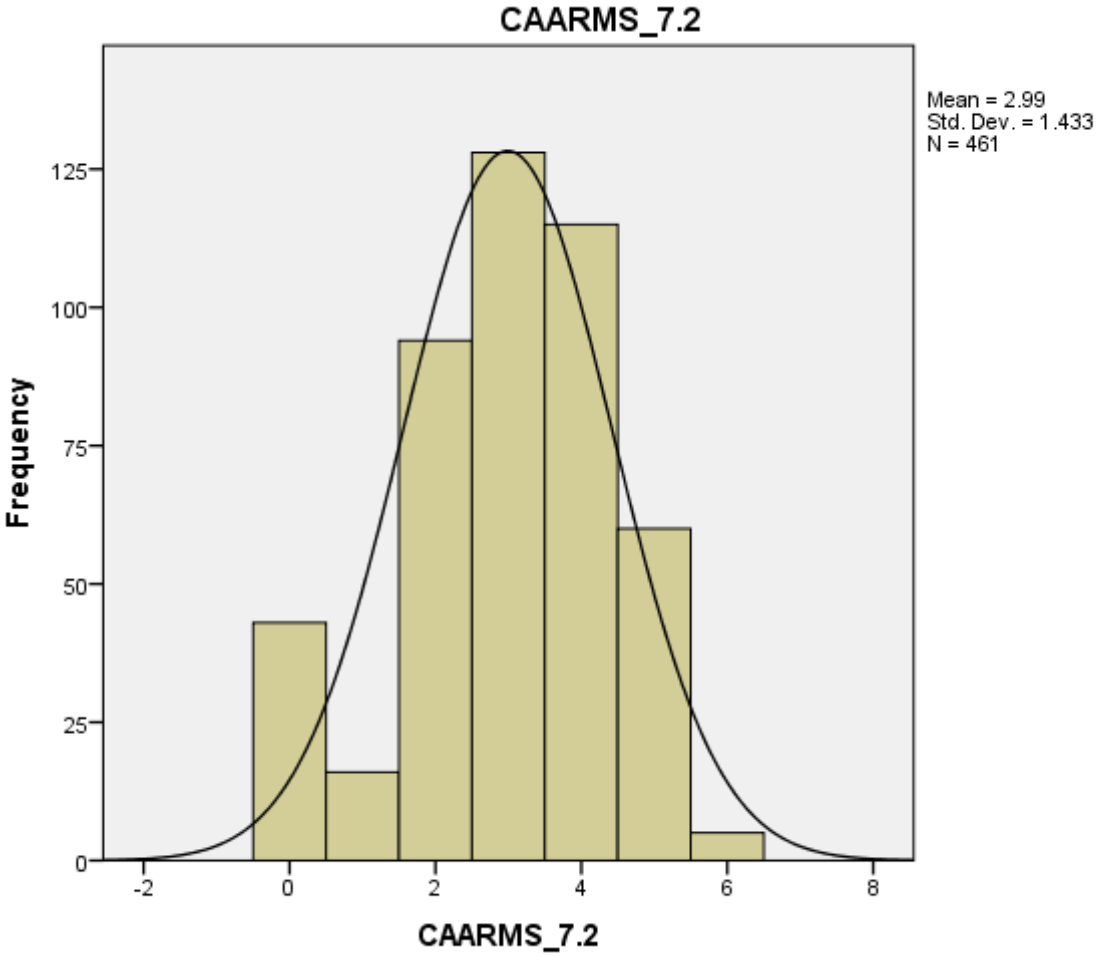

CAARMS_6.1
Mean = .51
Std. Dev. = .915
N = 461
Frequency
400
300
200
100
0
-1
0
1
2
3
4
5
CAARMS_6.1

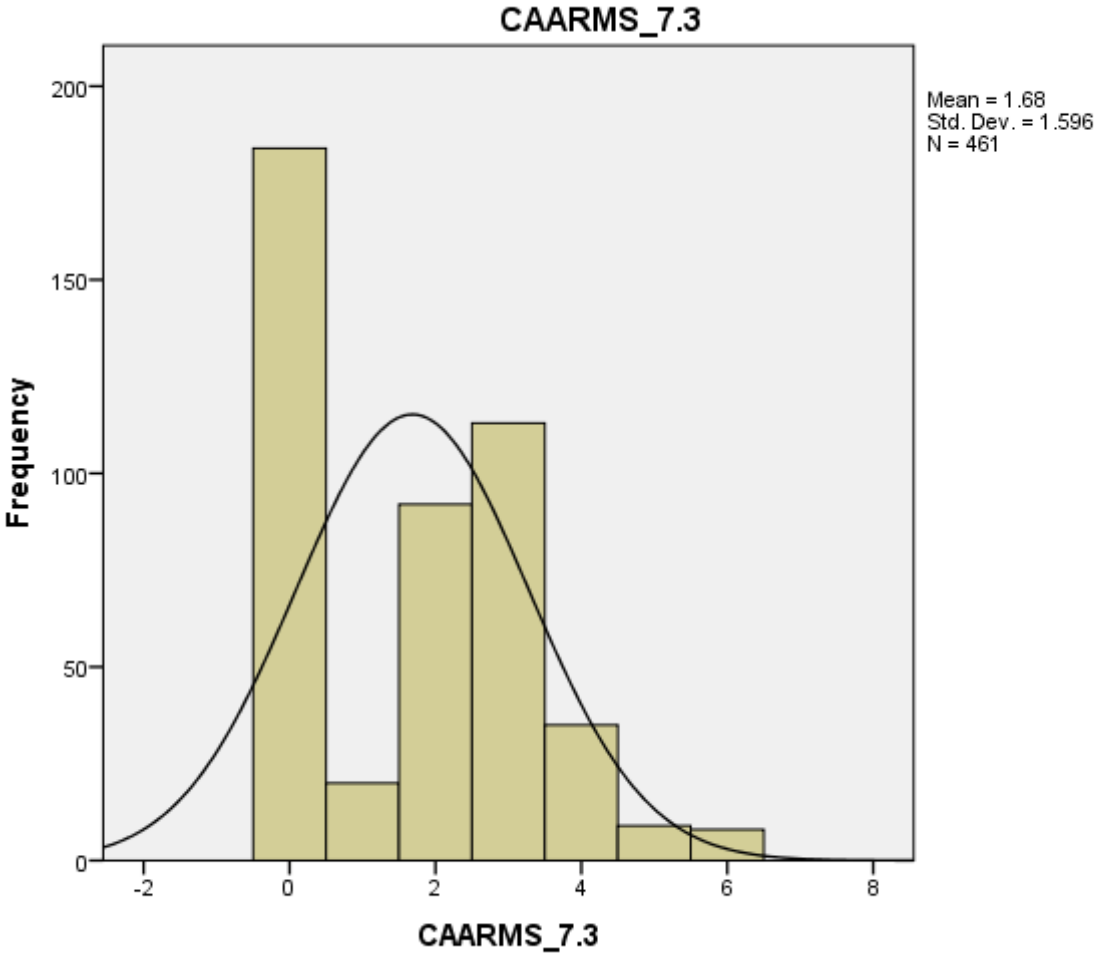

CAARMS_6.2
Mean = .12
Std. Dev. = .484
N = 461
Frequency
500
400
300
200
100
0
-1
0
1
2
3
4
5
CAARMS_6.2

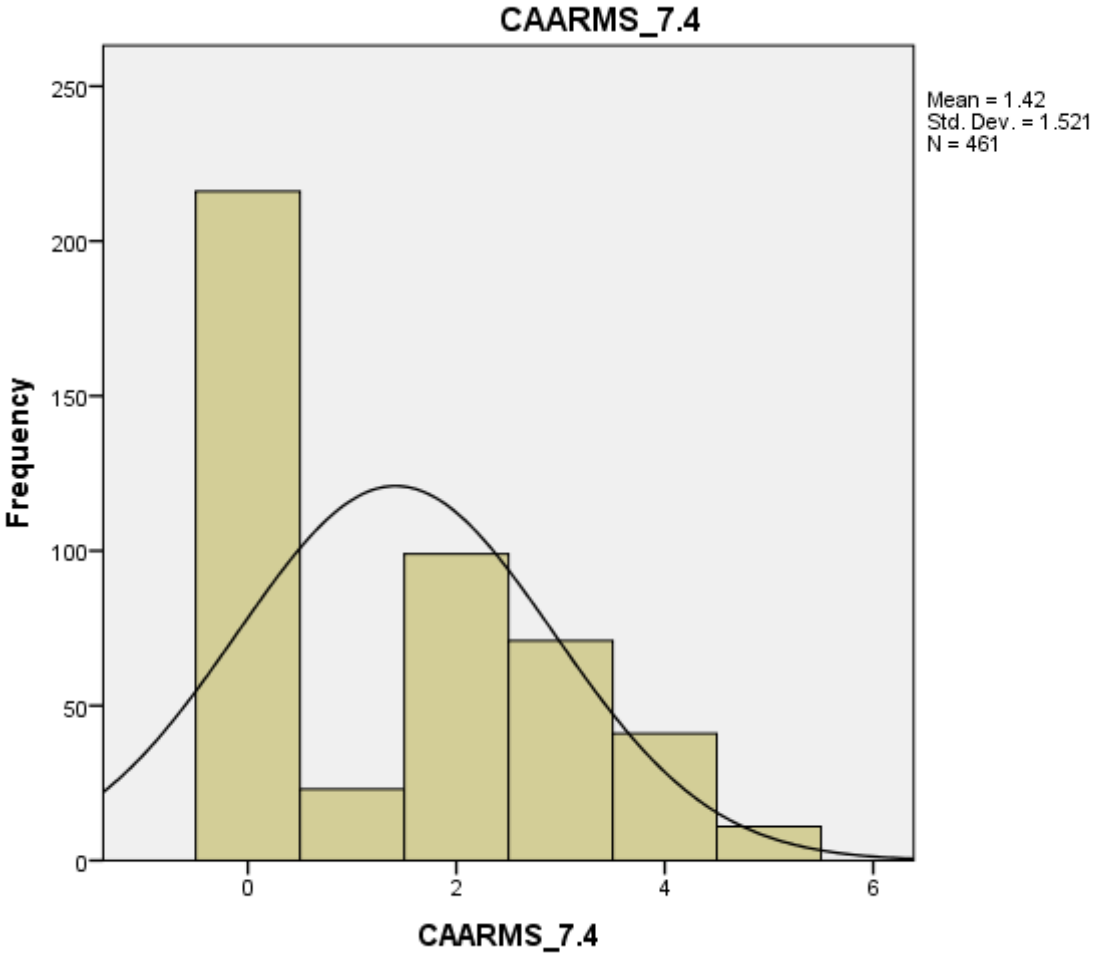

CAARMS_6.3
Mean = .64
Std. Dev. = 1.28
N = 461
Frequency
400
300
200
100
0
-2
0
2
4
6
8
CAARMS_6.3

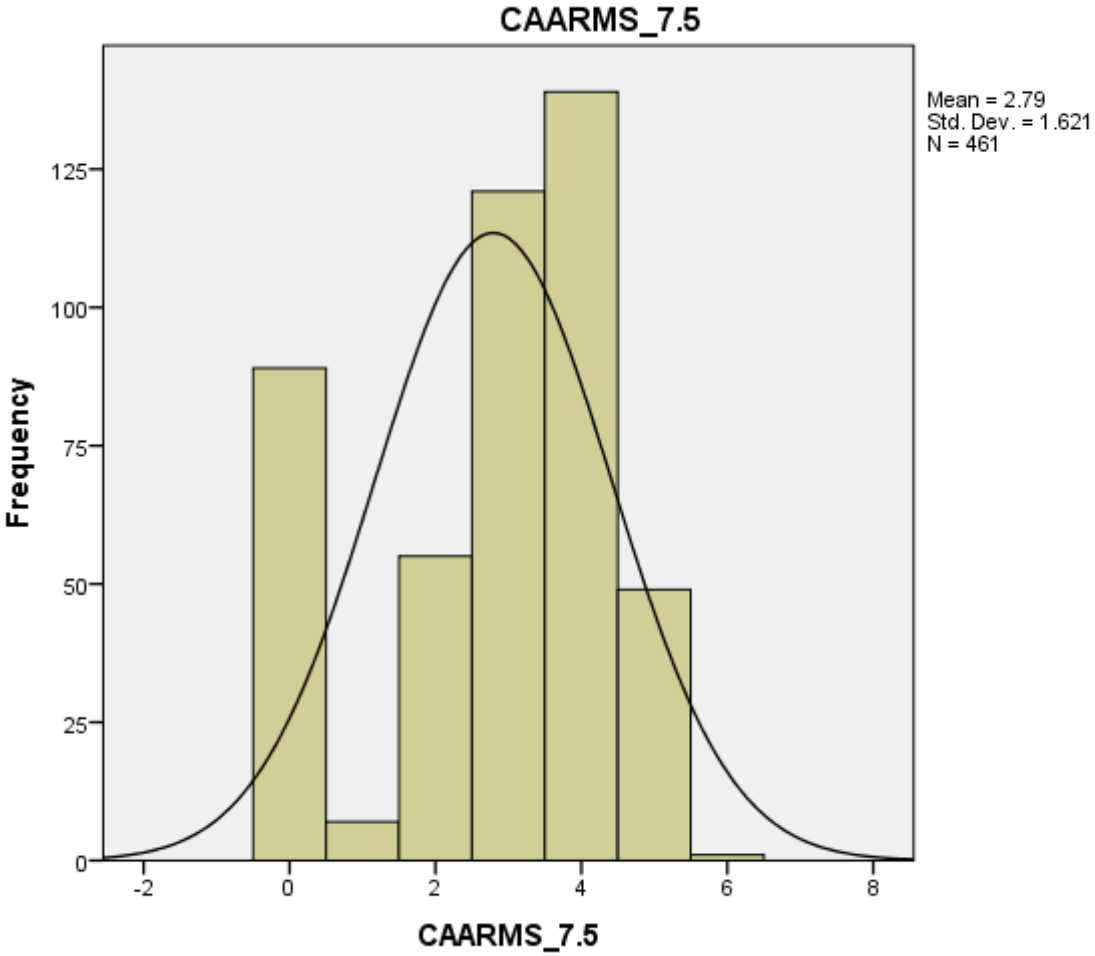

CAARMS_6.4
Mean = .85
Std. Dev. = 1.366
N = 461
Frequency
400
300
200
100
0
0
2
4
6
CAARMS_6.4

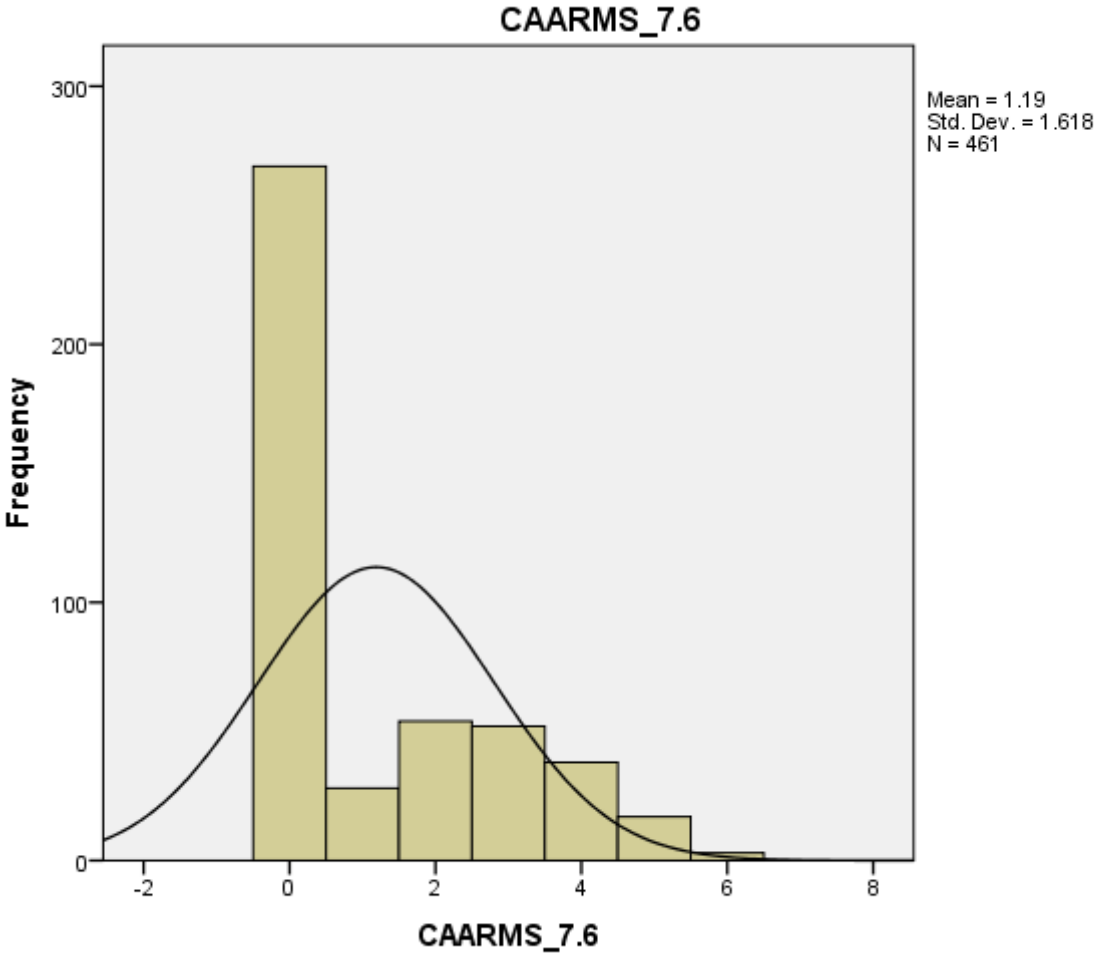

CAARMS_7.1
Mean = .68
Std. Dev. = 1.29
N = 461
Frequency
400
300
200
100
0
-2
0
2
4
6
8
CAARMS_7.1

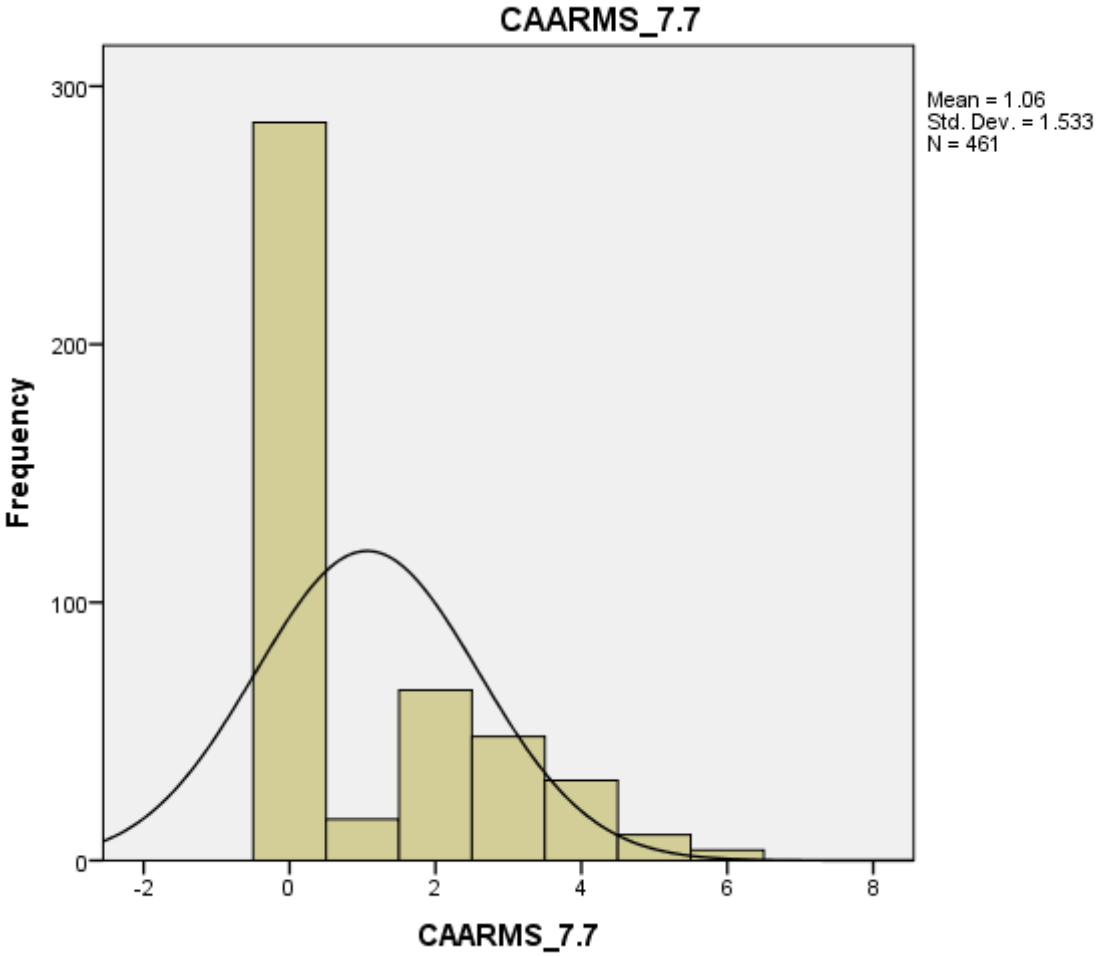

CAARMS_7.2
Mean = 2.99
Std. Dev. = 1.433
N = 461
Frequency
125
100
75
50
25
0
-2
0
2
4
6
8
CAARMS_7.2

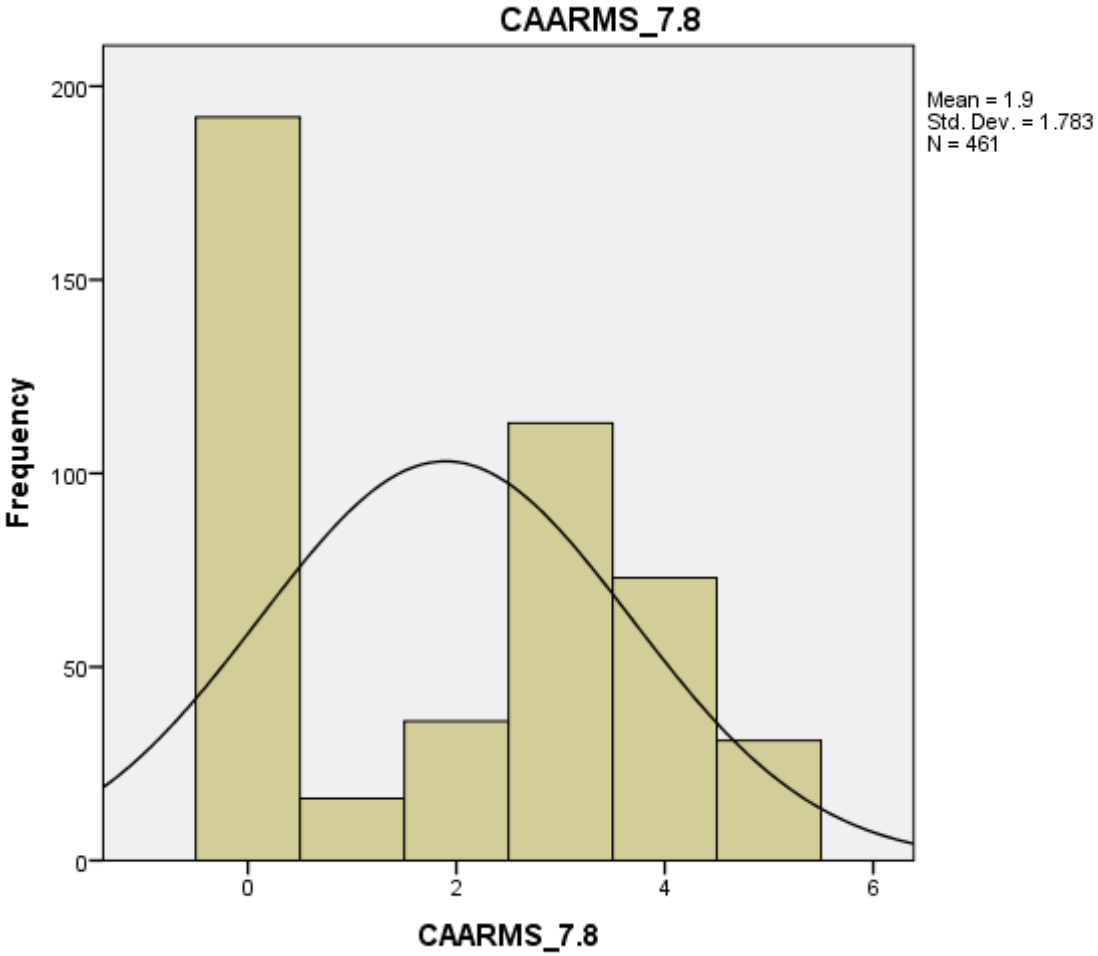

CAARMS_7.3
Mean = 1.68
Std. Dev. = 1.596
N = 461
Frequency
200
150
100
50
0
-2
0
2
4
6
8
CAARMS_7.3

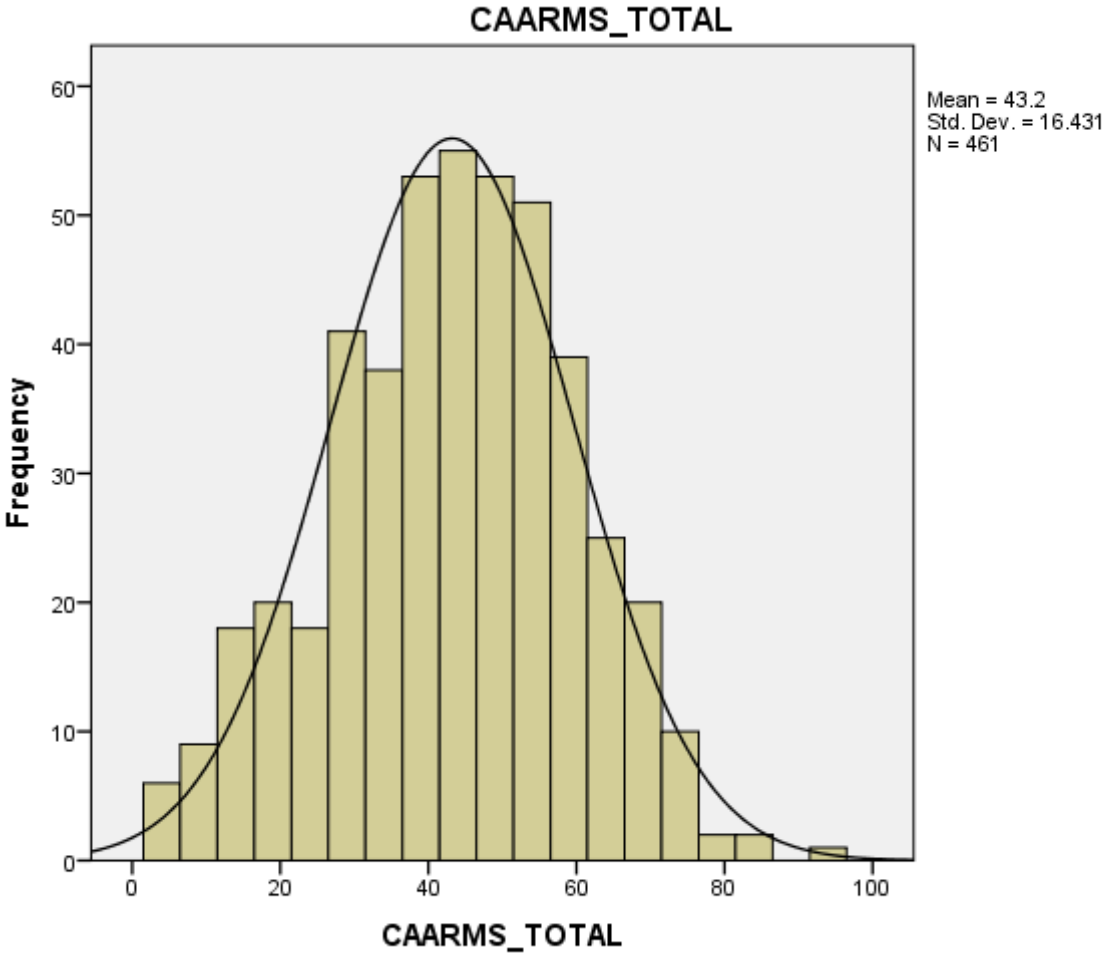

CAARMS_7.4
Mean = 1.42
Std. Dev. = 1.521
N = 461
Frequency
250
200
150
100
50
0
0
2
4
6
CAARMS_7.4


CAARMS_7.5
Mean = 2.79
Std. Dev. = 1.621
N = 461
Frequency
125
100
75
50
25
0
-2
0
2
4
6
8
CAARMS_7.5

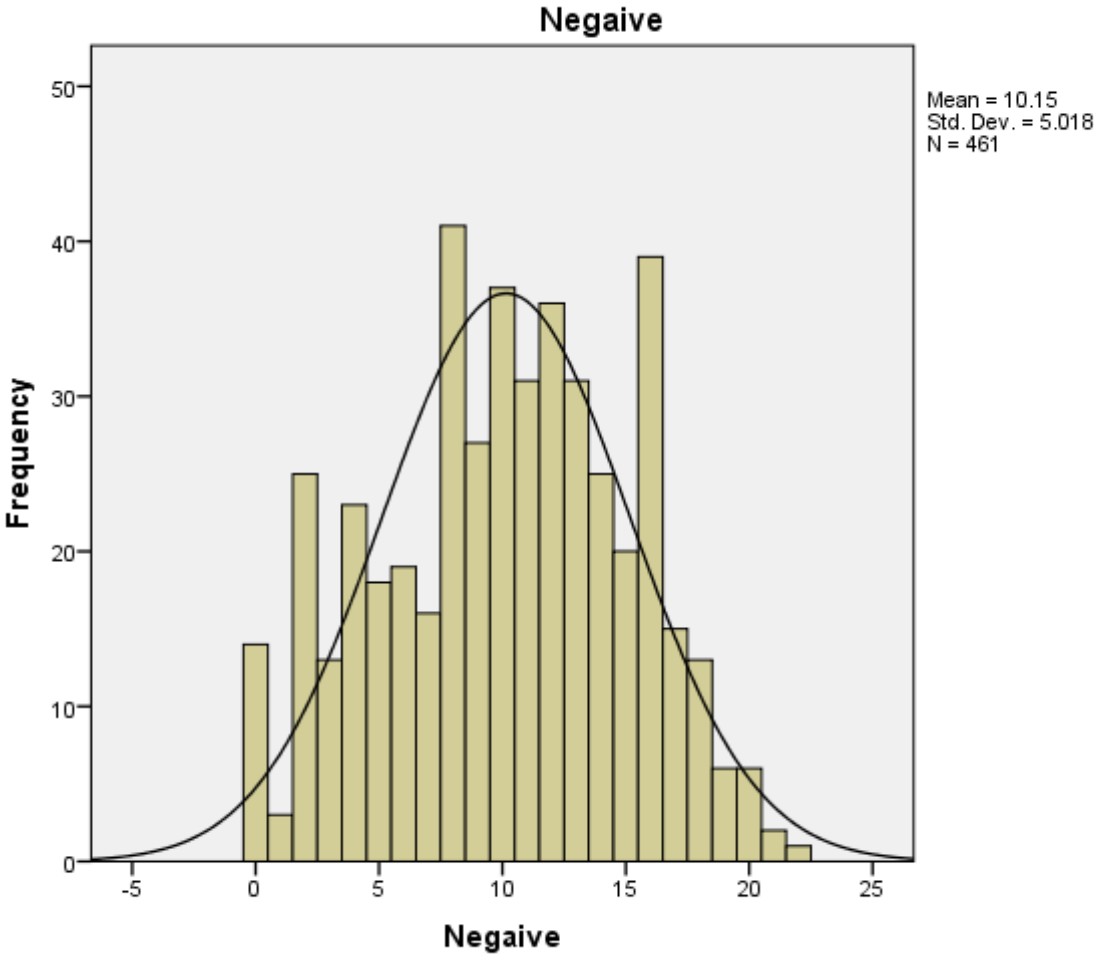

CAARMS_7.6
Mean = 1.19
Std. Dev. = 1.618
N = 461
Frequency
300
200
100
0
-2
0
2
4
6
8
CAARMS_7.6

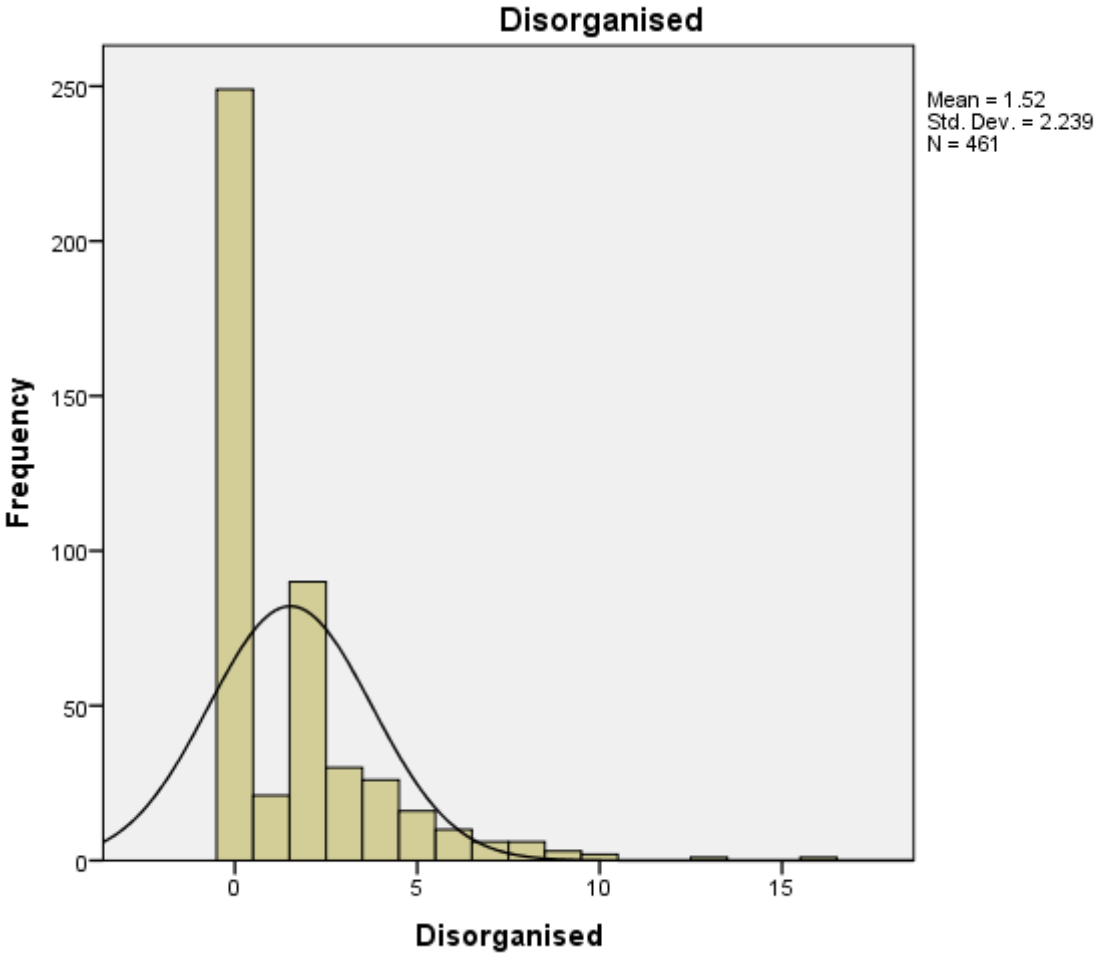

CAARMS_7.7
Mean = 1.06
Std. Dev. = 1.533
N = 461
Frequency
300
200
100
0
-2
0
2
4
6
8
CAARMS_7.7

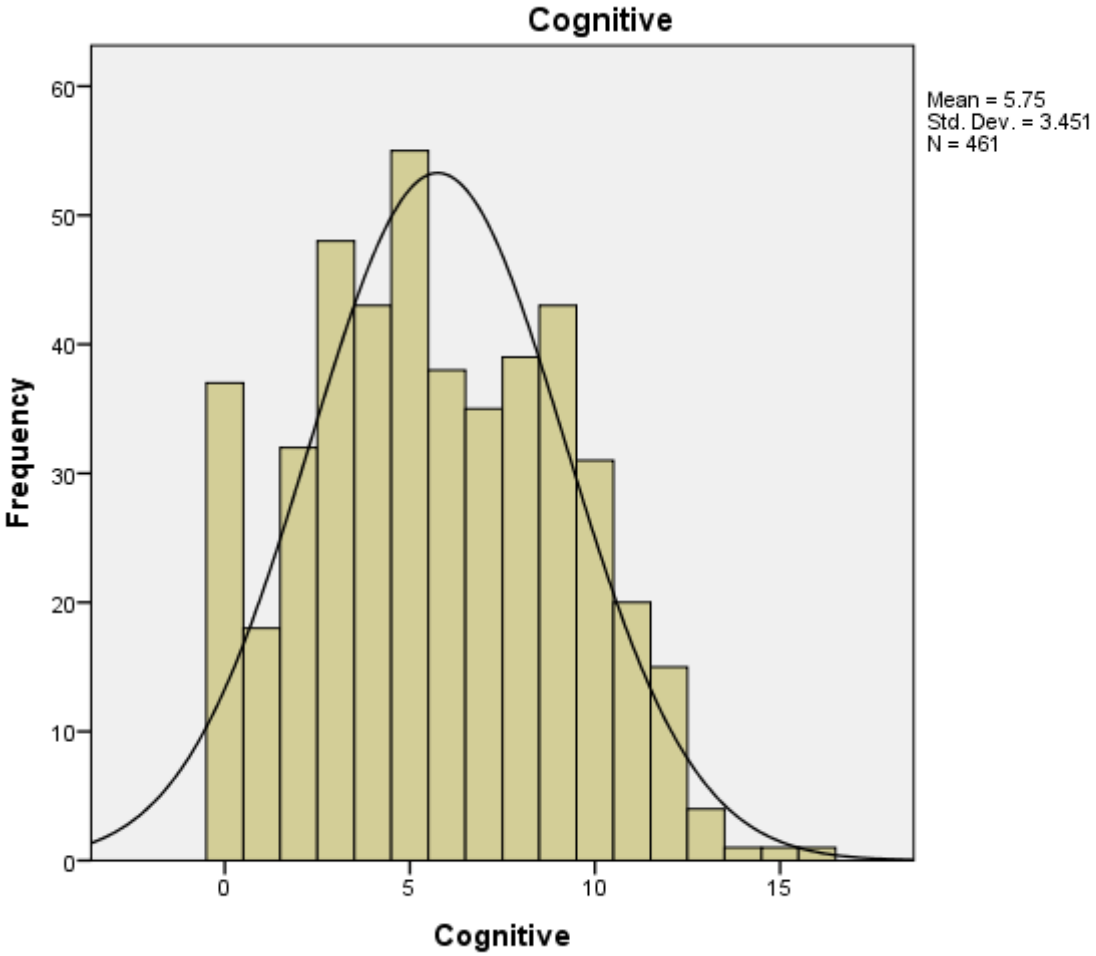

CAARMS_7.8
Mean = 1.9
Std. Dev. = 1.783
N = 461
Frequency
200
150
100
50
0
0
2
4
6
CAARMS_7.8

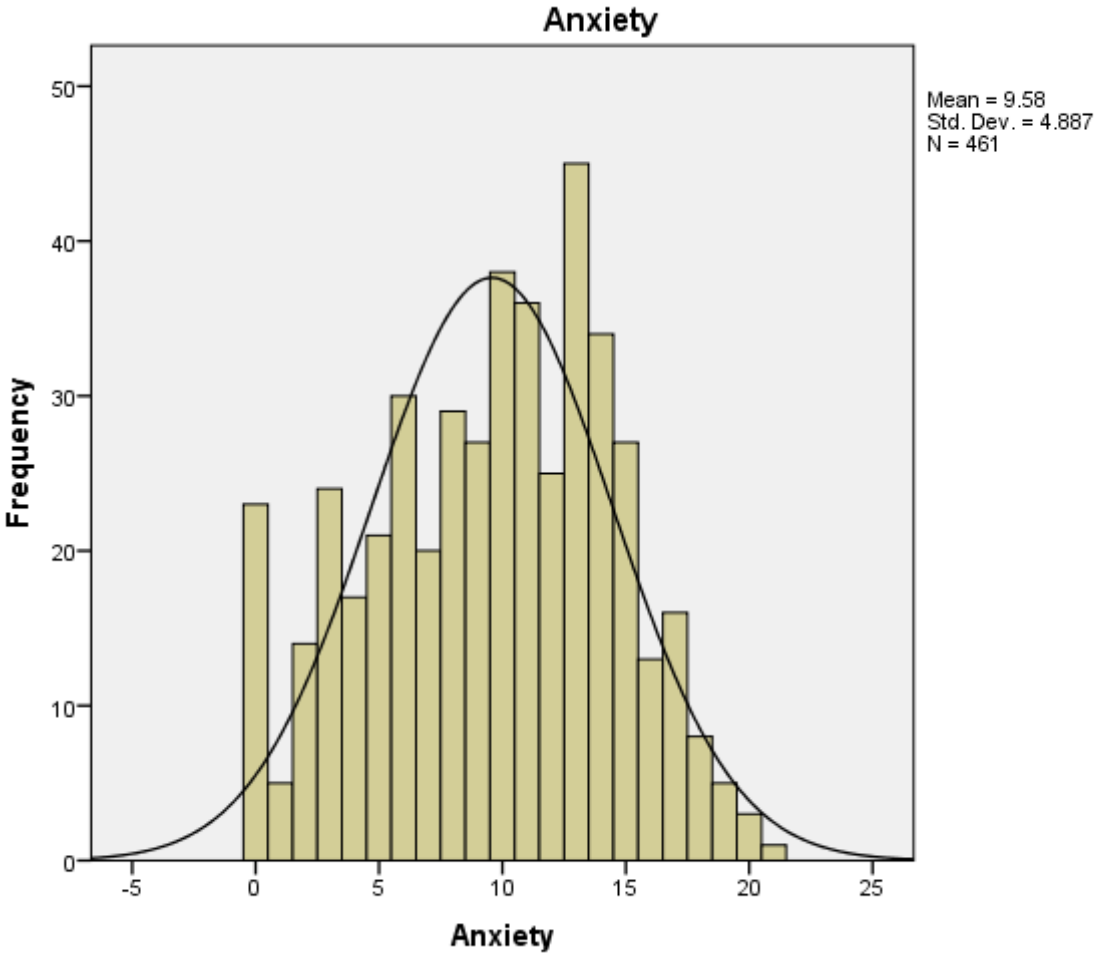

CAARMS_TOTAL
Mean = 43.2
Std. Dev. = 16.431
N = 461
Frequency
0
10
20
30
40
50
60
0
20
40
60
80
100
CAARMS_TOTAL

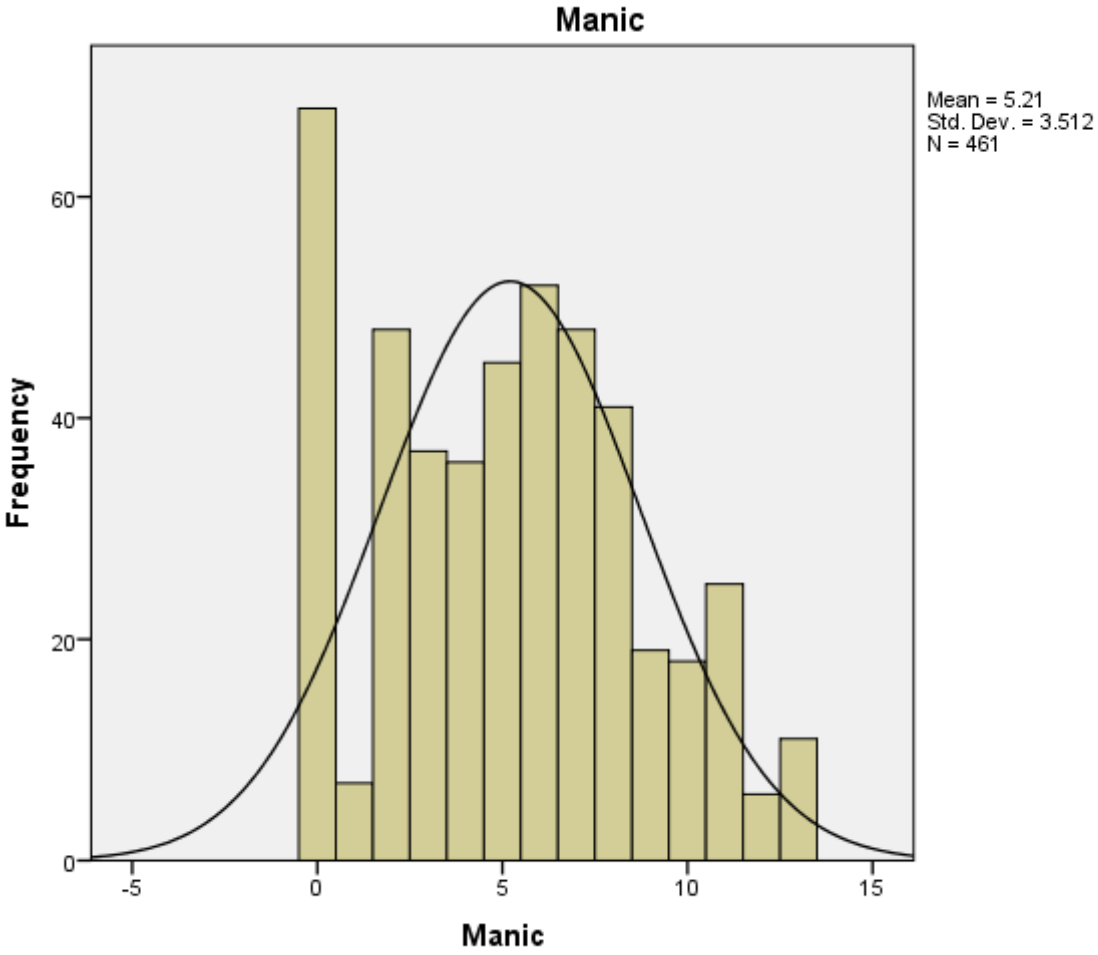
7.3 Appendix 3: Histograms of distribution of Composite scores for 5 Factors

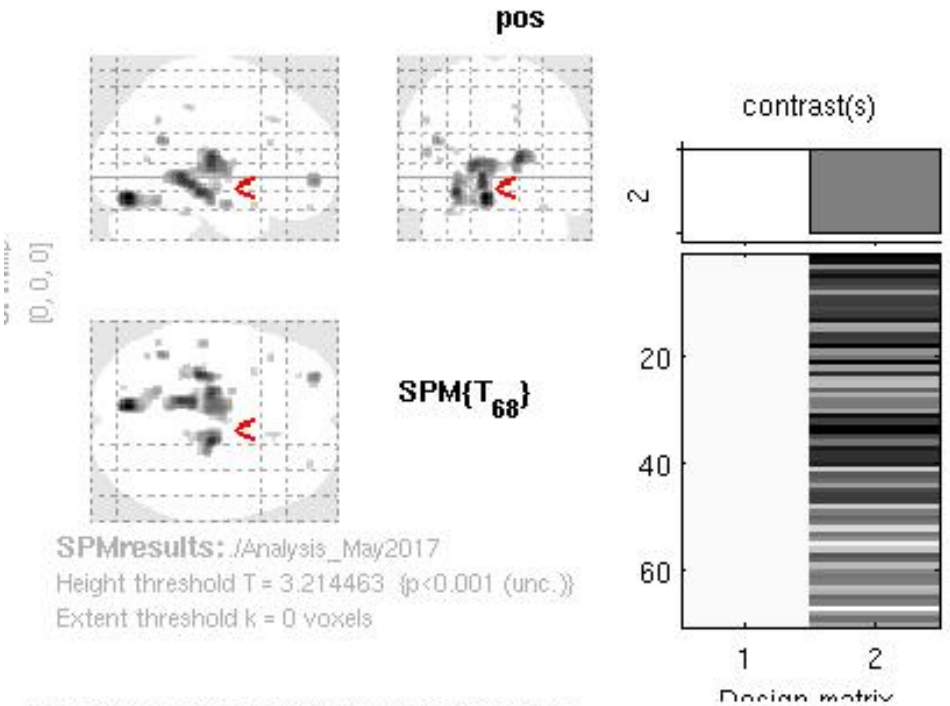



Disorganised
Mean = 1.52
Std. Dev. = 2.239
N = 461
Frequency
250
200
150
100
50
0
0
5
10
15
Disorganised


Cognitive
Mean = 5.75
Std. Dev. = 3.451
N = 461
Frequency
60
50
40
30
20
10
0
0
5
10
15
Cognitive


Anxiety
Mean = 9.58
Std. Dev. = 4.887
N = 461
Frequency
50
40
30
20
10
0
-5
0
5
10
15
20
25
Anxiety


Manic
Mean = 5.21
Std. Dev. = 3.512
N = 461
Frequency
60
40
20
0
-5
0
5
10
15
Manic



Statistics: ***p-values adjusted for search volume***

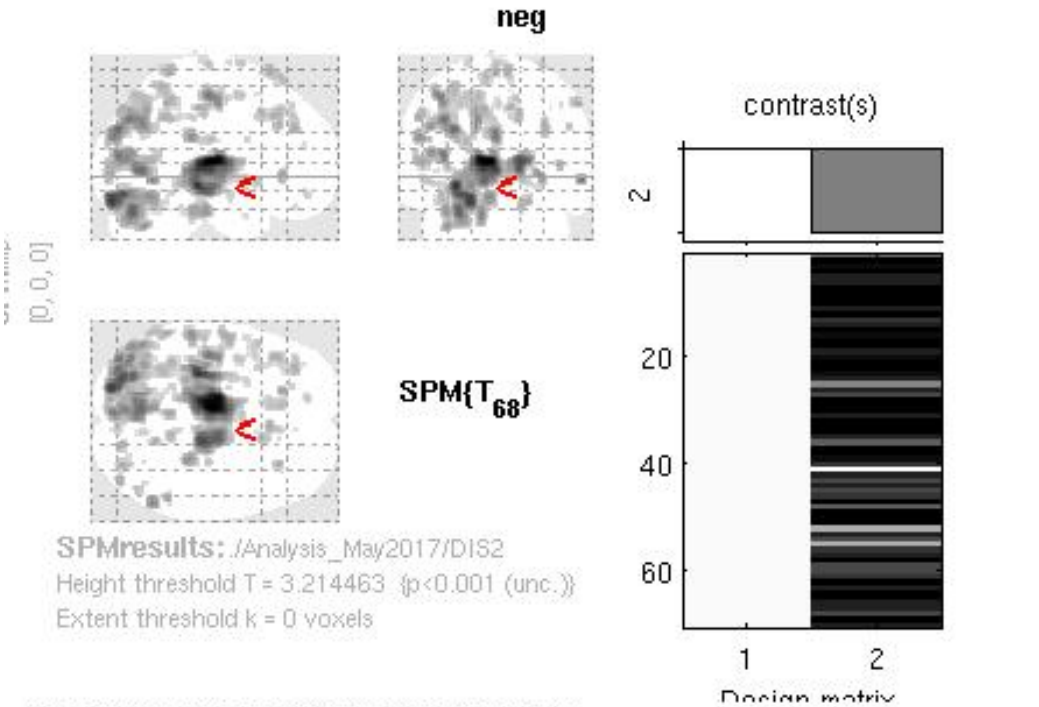
set-level		cluster-level				peak-level					mm mm mm		
p	c	p FWE-corr	q FDR-corr	k E	p uncorr	p FWE-corr	q FDR-corr	T (Z_e)		p uncorr			
0.000	20	0.283	0.717	278	0.096	0.130	0.572	4.45	4.15	0.000	-8	-78	-16
						0.789	0.907	3.56	3.40	0.000	-16	-58	-18
		0.369	0.717	222	0.133	0.270	0.572	4.17	3.92	0.000	16	-18	12
		0.391	0.717	210	0.143	0.298	0.572	4.13	3.88	0.000	-30	-26	-12
						0.865	0.907	3.46	3.30	0.000	-28	-36	0
		0.041	0.243	719	0.012	0.317	0.572	4.10	3.86	0.000	-10	-40	-2
						0.333	0.572	4.08	3.84	0.000	-10	-32	-8
						0.335	0.572	4.08	3.84	0.000	-16	-18	6
		0.866	0.892	31	0.581	0.646	0.907	3.72	3.54	0.000	-42	-52	22
		0.793	0.892	54	0.456	0.647	0.907	3.72	3.54	0.000	-28	54	-4
		0.824	0.892	44	0.504	0.725	0.907	3.64	3.46	0.000	-8	-8	-20
		0.884	0.892	25	0.625	0.850	0.907	3.48	3.33	0.000	-50	-24	14
		0.919	0.892	14	0.727	0.891	0.907	3.41	3.27	0.001	-18	-4	6
		0.937	0.892	8	0.803	0.910	0.907	3.38	3.23	0.001	-50	-56	36
		0.928	0.892	11	0.762	0.915	0.907	3.37	3.23	0.001	-34	-36	-26
						0.961	0.952	3.24	3.12	0.001	-26	-40	-26
		0.934	0.892	9	0.788	0.923	0.907	3.35	3.21	0.001	12	-34	46
		0.937	0.892	8	0.803	0.924	0.907	3.35	3.21	0.001	-40	24	20
		0.950	0.892	4	0.871	0.924	0.907	3.35	3.21	0.001	-40	-62	10
		0.937	0.892	8	0.803	0.929	0.907	3.34	3.20	0.001	12	26	36

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 3.21, p = 0.001 (0.968) Degrees of freedom = [1.0, 68.0]
Extent threshold: k = 0 voxels, p = 1.000 (0.968) FWHM = 18.0 22.2 19.4 mm mm mm; 9.0 11.1 9.7
Expected voxels per cluster, <k> = 103.192 Volume: 2272280 = 284035 voxels = 276.5 resels
Expected number of clusters, <c> = 3.45 Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 969.25
FWEp: 4.779, FDRp: Inf, FWEc: 719, FDRc: Inf Page 1

7.4 Appendix 4: Whole Brain Analysis of Correlation with Total CAARMS Scores

7.5 Appendix 5: Whole Brain Analysis of Correlation with Disorganised Symptom Dimension Scores



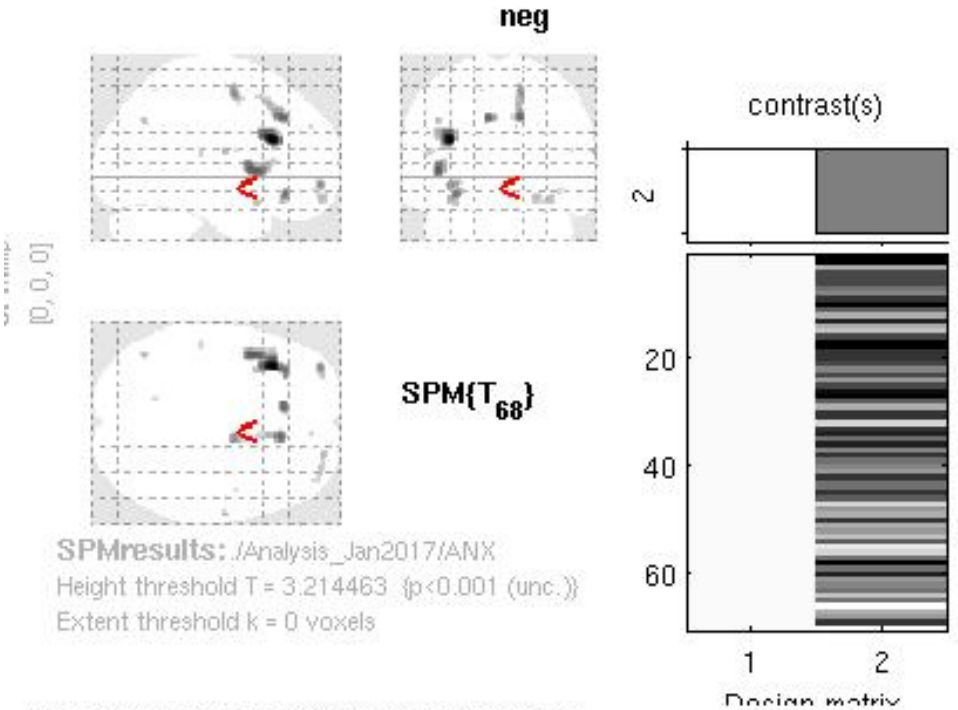
Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm		
p	c	p FWE-corr	q FDR-corr	k E	p uncorr	p FWE-corr	q FDR-corr	T (Z$_e$)		p uncorr			
0.000	58	0.000	0.001	29440	0.000	0.037	0.796	4.89	4.51	0.000	-8	-18	8
						0.146	0.923	4.42	4.13	0.000	-30	-28	-8
						0.213	0.923	4.28	4.01	0.000	16	-24	8
		0.003	0.017	13780	0.001	0.165	0.923	4.38	4.09	0.000	-20	-88	-18
						0.241	0.923	4.23	3.97	0.000	-26	-80	-14
						0.325	0.923	4.10	3.87	0.000	-28	-74	-26
		0.001	0.004	19640	0.000	0.356	0.923	4.06	3.83	0.000	-6	-68	2
						0.373	0.923	4.04	3.81	0.000	-32	-84	30
						0.440	0.923	3.96	3.75	0.000	-2	-86	26
		0.379	0.945	213	0.133	0.420	0.923	3.99	3.77	0.000	-38	-84	12
						0.625	0.923	3.76	3.57	0.000	-46	-74	14
						0.805	0.923	3.56	3.40	0.000	-42	-64	10
		0.449	0.945	179	0.166	0.458	0.923	3.94	3.73	0.000	-42	-20	52
		0.853	0.945	37	0.533	0.501	0.923	3.90	3.69	0.000	58	-60	-4
		0.607	0.945	116	0.260	0.628	0.923	3.76	3.57	0.000	-56	-34	26
						0.919	0.939	3.38	3.23	0.001	-56	-24	22
		0.792	0.945	56	0.437	0.727	0.923	3.65	3.48	0.000	-2	-48	70
		0.750	0.945	69	0.386	0.729	0.923	3.65	3.48	0.000	6	22	70
		0.850	0.945	38	0.527	0.729	0.923	3.65	3.48	0.000	-18	30	-2
		0.891	0.945	25	0.616	0.748	0.923	3.63	3.46	0.000	54	-50	48

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 3.21, p = 0.001 (0.973) Degrees of freedom = [1.0, 68.0]
Extent threshold: k = 0 voxels, p = 1.000 (0.973) FWHM = 17.7 21.9 19.1 mm mm mm; 8.8 11.0 9.6
Expected voxels per cluster, <k> = 98.684 Volume: 2272280 = 284035 voxels = 289.1 resels
Expected number of clusters, <c> = 3.59 Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 926.91
FWEp: 4.792, FDRp: Inf, FWEc: 1378, FDRc: 378

7.6 Appendix 6: Whole Brain Analysis of Correlation with Anxiety Symptom Dimension Scores



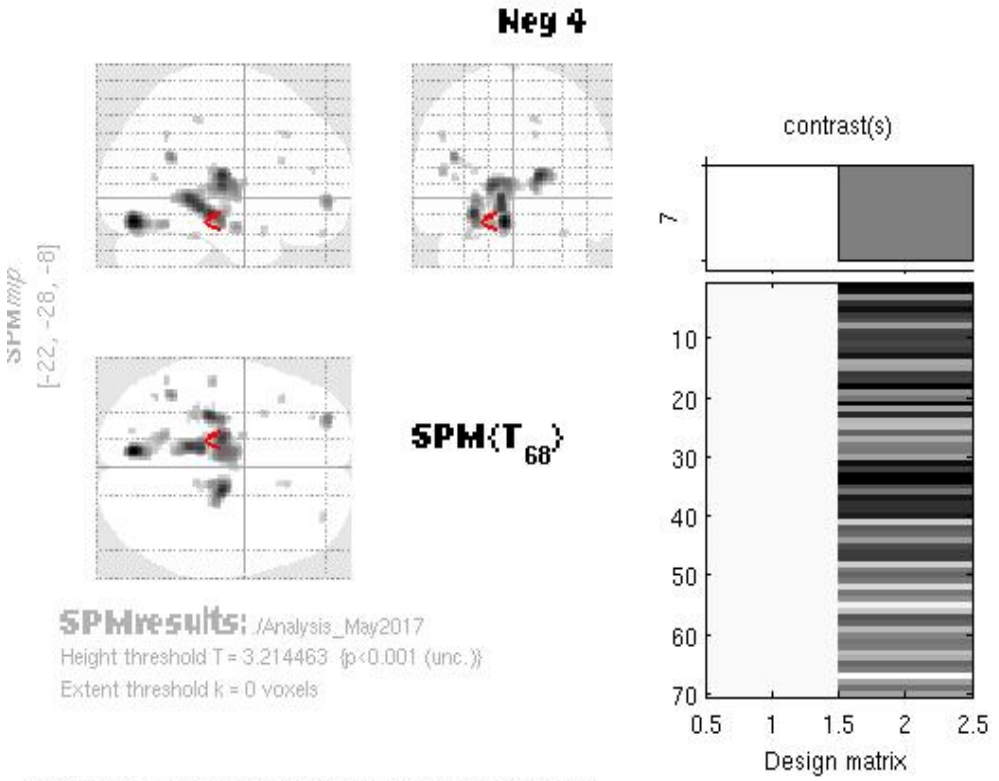
Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm	mm	mm
p	c	p FWE-corr	q FDR-corr	k E	p uncorr	p FWE-corr	q FDR-corr	T (Z)		p uncorr			
0.00016		0.382	0.948	183	0.176	0.229	0.989	4.14	3.90	0.000	-36	22	24
		0.545	0.948	111	0.288	0.535	0.989	3.74	3.56	0.000	-44	8	4
		0.803	0.948	30	0.594	0.575	0.989	3.70	3.52	0.000	-8	30	38
		0.659	0.948	72	0.394	0.580	0.989	3.69	3.51	0.000	12	28	38
						0.832	0.989	3.40	3.26	0.001	12	20	48
		0.792	0.948	33	0.574	0.626	0.989	3.65	3.47	0.000	-32	32	-14
		0.814	0.948	27	0.616	0.709	0.989	3.55	3.39	0.000	-34	56	-8
		0.781	0.948	36	0.556	0.731	0.989	3.53	3.37	0.000	14	-4	54
		0.903	0.948	5	0.854	0.833	0.989	3.40	3.26	0.001	64	-10	16
		0.818	0.948	26	0.623	0.851	0.989	3.37	3.23	0.001	24	58	-16
						0.871	0.989	3.34	3.20	0.001	34	56	-18
		0.899	0.948	6	0.837	0.866	0.989	3.35	3.21	0.001	-44	-66	36
		0.894	0.948	7	0.821	0.880	0.989	3.33	3.19	0.001	-32	12	-18
		0.925	0.948	1	0.948	0.913	0.989	3.27	3.14	0.001	10	50	32
		0.903	0.948	5	0.854	0.914	0.989	3.26	3.13	0.001	-50	-26	14
		0.908	0.948	4	0.873	0.918	0.989	3.25	3.13	0.001	40	54	-10
		0.919	0.948	2	0.918	0.927	0.989	3.24	3.11	0.001	-14	-60	56
		0.925	0.948	1	0.948	0.933	0.989	3.22	3.09	0.001	48	-2	16

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 3.21, p = 0.001 (0.935) Degrees of freedom = [1.0, 68.0]
Extent threshold: k = 0 voxels, p = 1.000 (0.978) M = 18.0 22.7 19.6 mm mm mm; 9.0 11.3 9.8
Expected voxels per cluster, <k> = 106.267 Volume: 1568904 = 196113 voxels = 173.6 resels
Expected number of clusters, <c> = 2.73 Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 998.14
FWEp: 4.686, FDRp: Inf, FWEc: Inf, FDRc: Inf

7.7 Appendix 7: ROI Analysis of Left Hippocampus and Total CAARMS score



Statistics: ***search volume: 6.0mm sphere at [-22,-28,-8]***

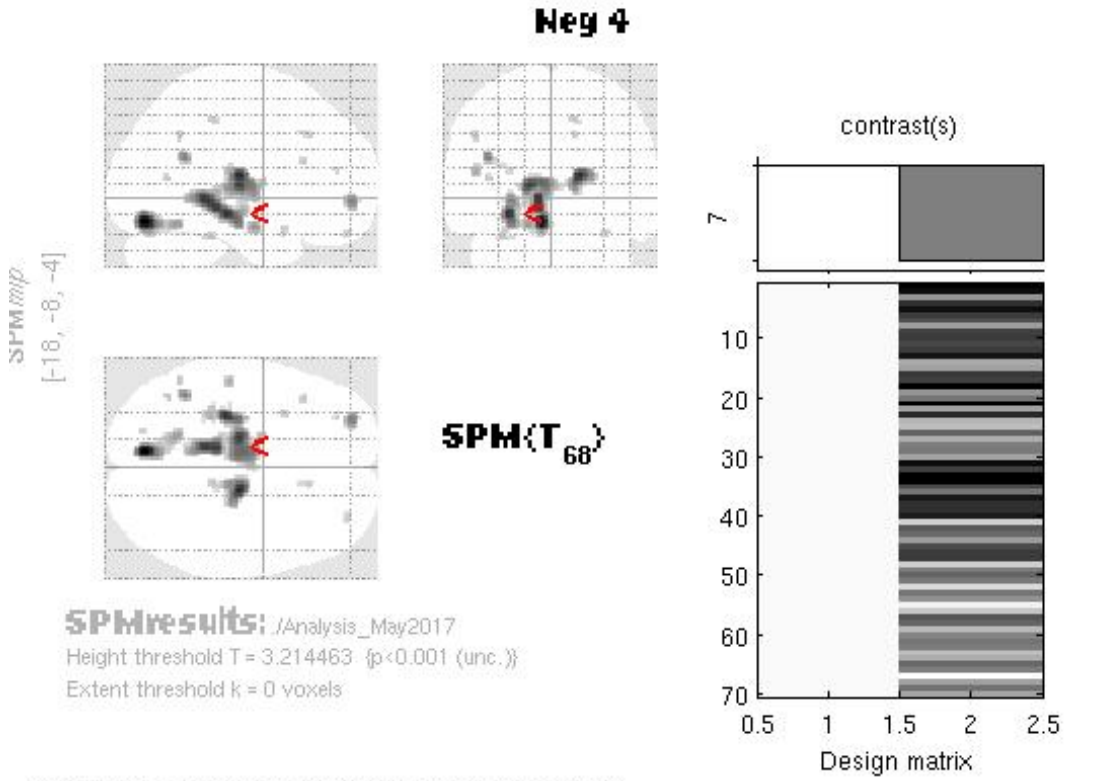
set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_e)	p_{uncorr}			
0.000	2	0.006	0.871	14	0.727	0.002	0.461	3.73	3.54	0.000	-28	-28	-8
		0.007	0.871	4	0.871	0.006	0.766	3.32	3.18	0.001	-18	-28	-12

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = 3.21, p = 0.001 (0.008)
Extent threshold: k = 0 voxels, p = 1.000 (0.008)
Expected voxels per cluster, <k> = 103.192
Expected number of clusters, <c> = 0.01
FWEp: 2.395, FDRp: Inf, FWEc: 4, FDRc: Inf

Degrees of freedom = [1.0, 68.0]
FWHM = 18.0 22.2 19.4 mm mm mm; 9.0 11.1 9.7 {voxels}
Volume: 984 = 123 voxels = 0.1 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 969.25 voxels)

7.8 Appendix 8: ROI Analysis of Left Pallidum and Total CAARMS score



Statistics: ***search volume: 6.0mm sphere at [-18,-8,-4]***

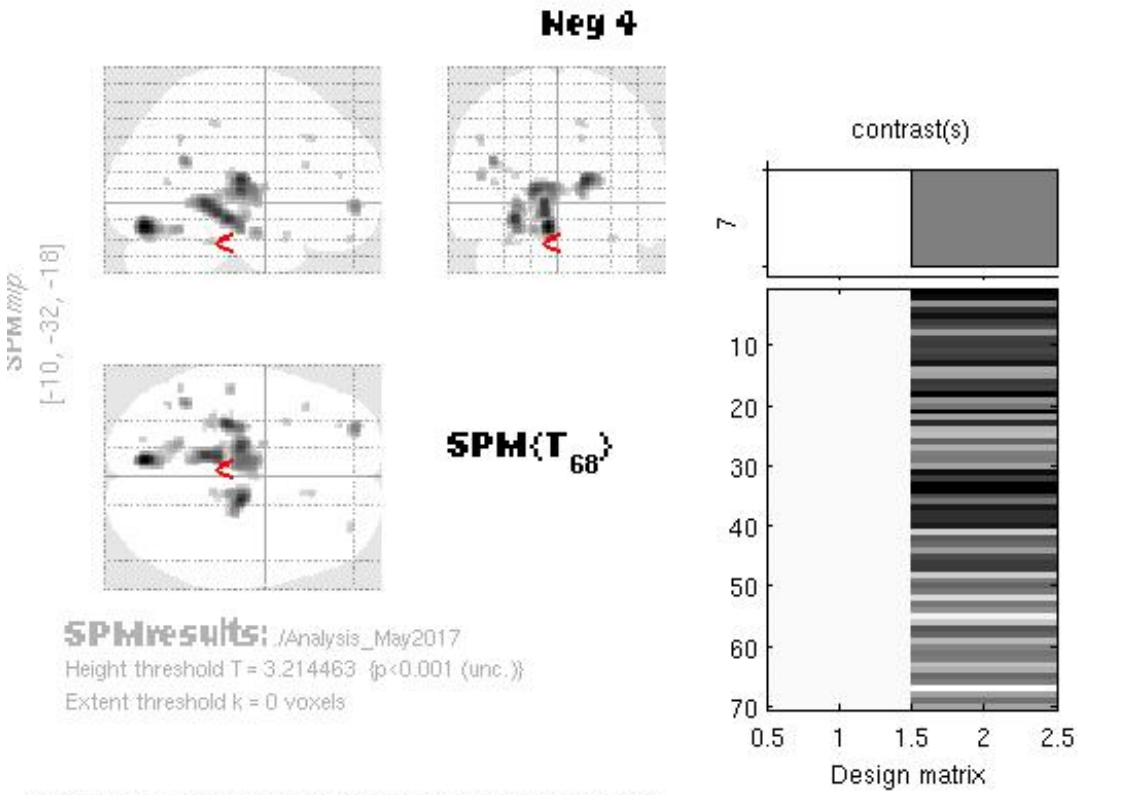
set-level p	set-level c	cluster-level				peak-level $p_{FWE-corr}$	peak-level $q_{FDR-corr}$	peak-level T	peak-level (Z_e)	peak-level p_{uncorr}	mm mm mm
		0.007	0.947	1	0.947	0.006	0.754	3.32	3.19	0.001	-18 -14 -4

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = 3.21, p = 0.001 (0.008)
Extent threshold: k = 0 voxels, p = 1.000 (0.008)
Expected voxels per cluster, <k> = 103.192
Expected number of clusters, <c> = 0.01
FWEp: 2.395, FDRp: Inf, FWEc: 1, FDRc: Inf

Degrees of freedom = [1.0, 68.0]
FWHM = 18.0 22.2 19.4 mm mm mm; 9.0 11.1 9.7 {voxels}
Volume: 984 = 123 voxels = 0.1 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 969.25 voxels)

7.9 Appendix 9: ROI Analysis of Left Midbrain and Total CAARMS score



Statistics: ***search volume: 6.0mm sphere at [-10,-32,-18]***

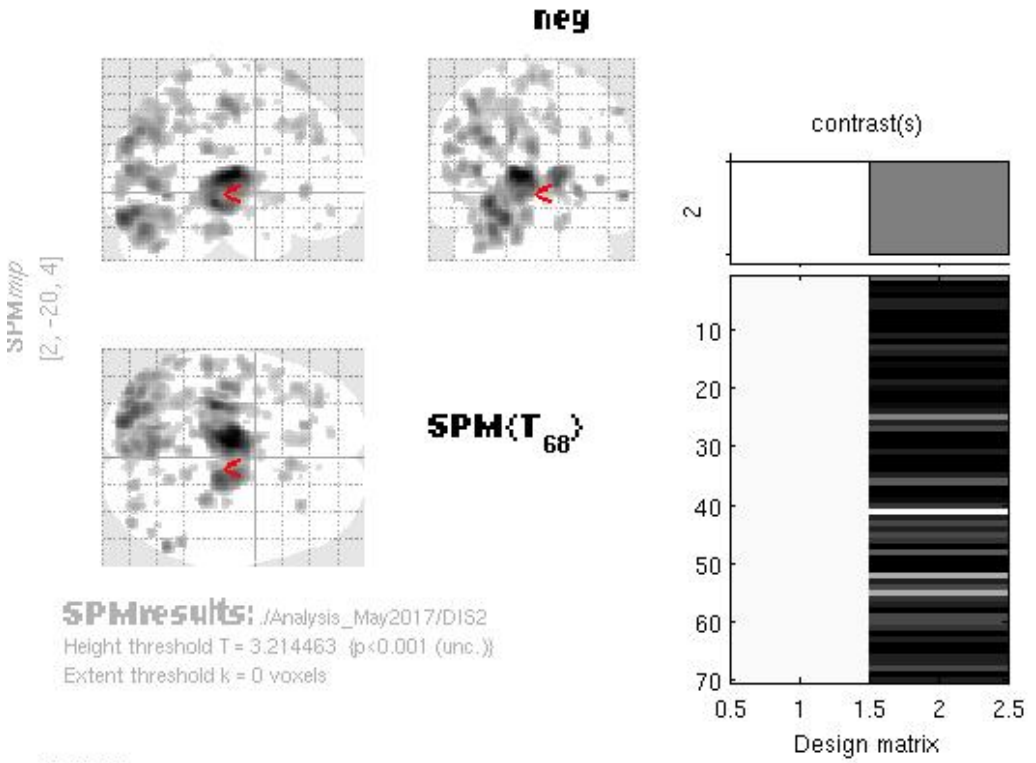
set-level		cluster-level			peak-level					mm mm mm
p	c				$p_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_e)	p_{uncorr}	
		0.007	0.947	1	0.947	0.005	0.629	3.39	3.25	0.001	-10 -32 -12

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = 3.21, p = 0.001 (0.008)
Extent threshold: k = 0 voxels, p = 1.000 (0.008)
Expected voxels per cluster, <k> = 103.192
Expected number of clusters, <c> = 0.01
FWEp: 2.395, FDRp: Inf, FWEc: 1, FDRc: Inf

Degrees of freedom = [1.0, 68.0]
FWHM = 18.0 22.2 19.4 mm mm mm; 9.0 11.1 9.7 (voxels)
Volume: 984 = 123 voxels = 0.1 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 969.25 voxels)

7.10 Appendix 10: ROI Analysis of Mediodorsal Thalamus and Disorganised – Behavioural Dimension



Statistics: ***search volume: 6.0mm sphere at [2,-20,4]***

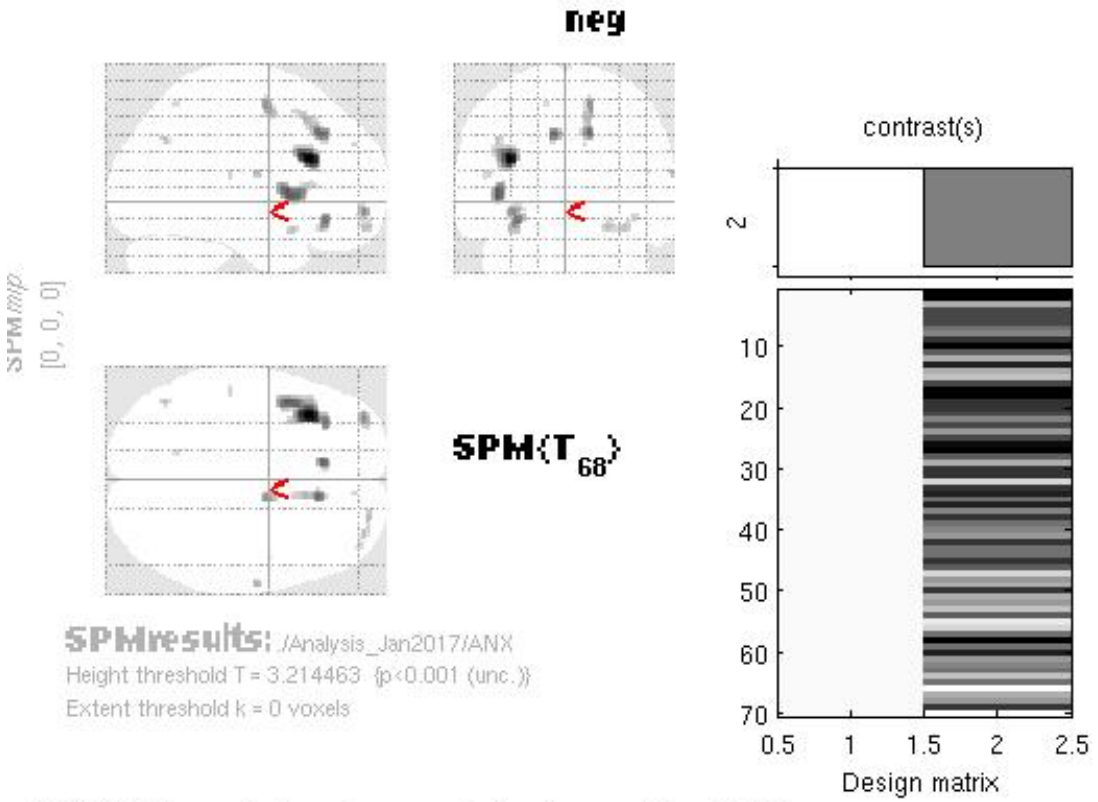
set-level		cluster-level				peak-level					mm mm mm
p	c					$p_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_e)	p_{uncorr}	
		0.002	0.313	93	0.313	0.000	0.071	4.37	4.09	0.000	-4 -20 4
						0.003	0.349	3.61	3.44	0.000	8 -20 4

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = 3.21, p = 0.001 (0.008)
Extent threshold: k = 0 voxels, p = 1.000 (0.008)
Expected voxels per cluster, <k> = 98.684
Expected number of clusters, <c> = 0.01
FWEp: 2.405, FDRp: Inf, FWEc: 93, FDRc: Inf

Degrees of freedom = [1.0, 68.0]
FWHM = 17.7 21.9 19.1 mm mm mm; 8.8 11.0 9.6 (voxels)
Volume: 984 = 123 voxels = 0.1 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 926.91 voxels)

7.11 Appendix 11: ROI Analysis of Insula and Anxiety Dimension



Statistics: ***search volume: image mask: ./insula_amygdal_mask.nii,1***

set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	T	(Z_e)	p_{uncorr}			
0.012	2	0.067	0.852	63	0.426	0.039	0.376	3.74	3.56	0.000	-44	8	4
						0.040	0.376	3.73	3.55	0.000	-44	12	2
		0.135	0.894	3	0.894	0.115	0.750	3.33	3.19	0.001	-32	12	-18

table shows 16 local maxima more than 4.0mm apart

Height threshold: T = 3.21, p = 0.001 (0.150)
Extent threshold: k = 0 voxels, p = 1.000 (0.150)
Expected voxels per cluster, <k> = 106.267
Expected number of clusters, <c> = 0.16
FWEp: 3.651, FDRp: Inf, FWEc: Inf, FDRc: Inf

Degrees of freedom = [1.0, 68.0]
FWHM = 18.0 22.7 19.6 mm mm mm; 9.0 11.3 9.8 {voxels}
Volume: 32200 = 4025 voxels = 2.0 resels
Voxel size: 2.0 2.0 2.0 mm mm mm; (resel = 998.14 voxels)